

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07K 14/445, C12N 15/30, A61K 39/015		A2	(11) International Publication Number: WO 96/40766
			(43) International Publication Date: 19 December 1996 (19.12.96)
(21) International Application Number: PCT/US96/09508		(74) Agent: ALTMAN, Daniel, E.; Knobbe, Martens, Olson and Bear, 16th floor, 620 Newport Center Drive, Newport Beach, CA 92660 (US).	
(22) International Filing Date: 7 June 1996 (07.06.96)			
(30) Priority Data: 08/487,826 7 June 1995 (07.06.95) US		(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(71) Applicant: THE GOVERNMENT OF THE UNITED STATES OF AMERICA, represented by THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES [US/US]; Office of Technology Transfer, National Institutes of Health, Suite 325, 6011 Executive Boulevard, Rockville, MD 20852-3804 (US).			
(72) Inventors: SIM, Kim, Lee; 308 Argosy Drive, Gaithersburg, MD 20878 (US). CHITNIS, Chetan; 3217 Wisconsin Avenue, No. 2B, Washington, DC 20016 (US). MILLER, Louis, H.; 5450 Whitley Park Terrace, No. 609, Bethesda, MD 20814 (US). PETERSON, David, S.; 315 Edmonston Drive, Rockville, MD 20851 (US). SU, Xin-Zhuan; Apartment 1122, 1001 Rockville Pike, Rockville, MD 20852 (US). WELLEMS, Thomas, E.; 1715 Wilmart Street, Rockville, MD 20852 (US).		Published <i>Without international search report and to be republished upon receipt of that report.</i>	
(54) Title: BINDING DOMAINS FROM PLASMODIUM VIVAX AND PLASMODIUM FALCIPARUM ERYTHROCYTE BINDING PROTEINS			
(57) Abstract <p>The present invention provides isolated polypeptides useful in the treatment and prevention of malaria caused by <i>Plasmodium falciparum</i> or <i>P. vivax</i>. In particular, the polypeptides are derived from the binding domains of the proteins in the DBL family as well as the sialic acid binding protein (SABP) on <i>P. falciparum</i> merozoites. The polypeptides may also be derived from the Duffy antigen binding protein (DABP) on <i>P. vivax</i> merozoites.</p>			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

**BINDING DOMAINS FROM *PLASMODIUM VIVAX* AND
PLASMODIUM FALCIPARUM ERYTHROCYTE BINDING PROTEINS**

BACKGROUND OF THE INVENTION

5 Malaria infects 200 - 400 million people each year causing 1-2 million deaths, thus remaining one of the most important infectious diseases in the world. Approximately 25 percent of all deaths of children in rural Africa between the ages of one and four years are caused by malaria. Due to the importance of the disease as a worldwide health problem, considerable effort is being expended to identify and develop malaria vaccines.

Malaria in humans is caused by four species of the parasite *Plasmodium*: *P. falciparum*, *P. vivax*, *P. knowlesi* and *P. malariae*. The major cause of malaria in humans is *P. falciparum* which infects 200 million to 10 400 million people every year, killing 1 to 4 million.

Duffy Antigen Binding Protein (DABP) and Sialic Acid Binding Protein (SABP) are soluble proteins that appear in the culture supernatant after infected erythrocytes release merozoites. Immunochemical data indicate that DABP and SABP which are the respective ligands for the *P. vivax* and *P. falciparum* Duffy and sialic acid receptors on erythrocytes, possess specificities of binding which are identical either in soluble or membrane bound 15 form.

DABP is a 135 kDa protein which binds specifically to Duffy blood group determinants (Wertheimer *et al.*, Exp. Parasitol. 69: 340-350 (1989); Barnwell, *et al.*, J. Exp. Med. 169: 1795-1802 (1989)). Thus, binding of DABP is specific to human Duffy positive erythrocytes. There are four major Duffy phenotypes for human erythrocytes: Fy(a), Fy(b), Fy(ab) and Fy(negative), as defined by the anti-Fy^a and anti-Fy^b sera (Hadley *et al.*, In Red Cell Antigens and Antibodies, G. Garratty, ed. (Arlington, Va.:American Association of Blood Banks) pp. 17-33 (1986)). 20 DABP binds equally to both Fy(a) and Fy(b) erythrocytes which are equally susceptible to invasion by *P. vivax*; but not to Fy(negative) erythrocytes.

In the case of SABP, a 175kDa protein, binding is specific to the glycophorin sialic acid residues on erythrocytes (Camus and Hadley, *Science* 230:553-556 (1985); Orlandi, *et al.*, *J. Cell Biol.* 116:901-909 (1992)). 25 Thus, neuraminidase treatment (which cleaves off sialic acid residues) render erythrocytes immune to *P. falciparum* invasion.

The specificities of binding and correlation to invasion by the parasite thus indicate that DABP and SABP are the proteins of *P. vivax* and *P. falciparum* which interact with sialic acids and the Duffy antigen on the erythrocyte. The genes encoding both proteins have been cloned and the DNA and predicted protein sequences have been determined (B. Kim Lee Sim, *et al.*, *J. Cell Biol.* 111: 1877-1884 (1990); Fang, X., *et al.*, *Mol. Biochem Parasitol.* 44: 125-132 (1991)). 30

Despite considerable research efforts worldwide, because of the complexity of the *Plasmodium* parasite and its interaction with its host, it has not been possible to discover a satisfactory solution for prevention or abatement of the blood stage of malaria. Because malaria is a such a large worldwide health problem, there is a need for methods that abate the impact of this disease. The present invention provides effective preventive and 35 therapeutic measures against *Plasmodium* invasion.

SUMMARY OF THE INVENTION

5 The present invention provides compositions comprising an isolated DABP binding domain polypeptides and/or isolated SABP binding domain polypeptides. The DABP binding domain polypeptides preferably comprise between about 200 and about 300 amino acid residues while the SABP binding domain polypeptides preferably comprises between about 200 and about 600 amino acid residues. A preferred DABP binding domain polypeptide has about 325 residues of the amino acid sequence found in SEQ ID NO:2. A preferred SABP binding domain polypeptide has about 616 residues of the amino acid sequence of SEQ ID NO:4, encoded by the DNA sequence of SEQ ID NO: 3. The preferred DABP binding domain and SABP binding domain include the cysteine-rich portions of the proteins shown in Figure 1.

10 The present invention also includes pharmaceutical compositions comprising a pharmaceutically acceptable carrier and an isolated DABP binding domain polypeptide in an amount sufficient to induce a protective immune response to *Plasmodium vivax* merozoites in an organism. In addition, isolated SABP binding domain polypeptide in an amount sufficient to induce a protective immune response to *Plasmodium falciparum* may be added to the pharmaceutical composition.

15 Also provided are pharmaceutical compositions comprising a pharmaceutically acceptable carrier and an isolated SABP binding domain polypeptide in an amount sufficient to induce a protective immune response to *Plasmodium falciparum* merozoites in an organism. In addition, isolated DABP binding domain polypeptide in an amount sufficient to induce a protective immune response to *Plasmodium vivax* may be added to the pharmaceutical composition.

20 Isolated polynucleotides which encode a DABP binding domain polypeptides or SABP binding domain polypeptides are also disclosed. In addition, the present invention includes a recombinant cell comprising the polynucleotide encoding the DABP binding domain polypeptide.

25 The current invention further includes methods of inducing a protective immune response to *Plasmodium* merozoites in a patient. The methods comprise administering to the patient an immunologically effective amount of a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an isolated DABP binding domain polypeptide, an SABP binding domain polypeptide or a combination thereof.

30 The present disclosure also provides DNA sequences from additional *P. falciparum* genes in the Duffy-binding like (DBL) family that have regions conserved with the *P. falciparum* 175 kD and *P. vivax* 135 kD binding proteins.

DEFINITIONS

35 As used herein a "DABP binding domain polypeptide" or a "SABP binding domain polypeptide" are polypeptides substantially identical (as defined below) to a sequence from the cysteine-rich, amino-terminal region of the Duffy antigen binding protein (DABP) or sialic acid binding protein (SABP), respectively. Such polypeptides are capable of binding either the Duffy antigen or sialic acid residues on glycophorin. In particular, DABP binding domain polypeptides consist of amino acid residues substantially similar to a sequence of SABP within a binding domain

containing the cysteine-rich sequence shown in Figure 1. SABP binding domain polypeptides consist of residues substantially similar to a sequence of DABP within a binding domain containing the cysteine-rich sequence shown in Figure 1.

5 The binding domain polypeptides encoded by the genes of the *DBL* family consist of those residues substantially identical to the sequence of the binding domains of DABP and SABP as defined above. The DBL family comprises sequences with substantial similarity to the conserved regions of the DABP and SABP. These include those sequences reported here as *ebf-1* (SEQ ID NO:5 and SEQ ID NO:6), E31a (SEQ ID NO:7 and SEQ ID NO:8), *var-7* (SEQ. ID. NO:13 and SEQ. ID. NO:14, GenBank Accession No. L42636) and *var-1* (SEQ. ID. NO:15 and SEQ ID NO:16, GenBank Accession No. L40608). The sequence *ebf-2*, (SEQ ID NO:9 and SEQ ID NO:10) represents the
10 binding domains of *var-7*, and Proj3 (SEQ ID NO:11 and SEQ ID NO:12) is the binding domain of *var-1*. The DBL family also includes two other members *var-2* and *var-3* (GenBank Accession No. L40609).

The polypeptides of the invention can consist of the full length binding domain or a fragment thereof. Typically DABP binding domain polypeptides will consist of from about 50 to about 325 residues, preferably between about 75 and 300, more preferably between about 100 and about 250 residues. SABP binding domain
15 polypeptides will consist of from about 50 to about 616 residues, preferably between about 75 and 300, more preferably between about 100 and about 250 residues.

Particularly preferred polypeptides of the invention are those within the binding domain that are conserved between SABP and the *DBL* family. Residues within these conserved domains are shown in Figure 1, below.

20 Two polynucleotides or polypeptides are said to be "identical" if the sequence of nucleotides or amino acid residues in the two sequences is the same when aligned for maximum correspondence. Optimal alignment of sequences for comparison may be conducted by the local homology algorithm of Smith and Waterman *Adv. Appl. Math.* 2: 482 (1981), by the homology alignment algorithm of Needleman and Wunsch *J. Mol. Biol.* 48:443 (1970), by the search for similarity method of Pearson and Lipman *Proc. Natl. Acad. Sci. (U.S.A.)* 85: 2444 (1988), by
25 computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, WI), or by inspection. The term "substantial identity" means that a polypeptide comprises a sequence that has at least 80% sequence identity, preferably 90%, more preferably 95% or more, compared to a reference sequence over a comparison window of about 20 residues to about 600 residues-- typically about 50 to about 500 residues usually about 250 to 300
30 residues. The values of percent identity are determined using the programs above. Particularly preferred peptides of the present invention comprise a sequence in which at least 70% of the cysteine residues conserved in DABP and SABP are present. Additionally, the peptide will comprise a sequence in which at least 50% of the tryptophan residues conserved in DABP and SABP are present. The term substantial similarity is also specifically defined here with respect to those amino acid residues found to be conserved between DABP, SABP and the sequences of the
35 DBL family. These conserved amino acids consist prominently of tryptophan and cysteine residues conserved among all sequences reported here. In addition the conserved amino acid residues include phenylalanine residues which may

be substituted with tyrosine. These amino acid residues may be determined to be conserved after the sequences have been aligned using methods outlined above by someone skilled in the art.

Another indication that polypeptide sequences are substantially identical is if one protein is immunologically reactive with antibodies raised against the other protein. Thus, the polypeptides of the invention include polypeptides immunologically reactive with antibodies raised against the SABP binding domain, the DABP binding domain or raised against the conserved regions of the *DBL* family.

Another indication that nucleotide sequences are substantially identical is if two molecules hybridize to each other under stringent conditions. Stringent conditions are sequence dependent and will be different in different circumstances. Generally, stringent conditions are selected to be about 5° C lower than the thermal melting point (T_m) for the specific sequence at a defined ionic strength and pH. The T_m is the temperature (under defined ionic strength and pH) at which 50% of the target sequence hybridizes to a perfectly matched probe. Typically, stringent conditions will be those in which the salt concentration is about 0.02 molar at pH 7 and the temperature is at least about 60°C.

Nucleotide sequences are also substantially identical for purposes of this application when the polypeptides which they encode are substantially identical. Thus, where one nucleic acid sequence encodes essentially the same polypeptide as a second nucleic acid sequence, the two nucleic acid sequences are substantially identical, even if they would not hybridize under stringent conditions due to silent substitutions permitted by the genetic code (*see, Darnell et al. (1990) Molecular Cell Biology, Second Edition Scientific American Books, W.H. Freeman and Company, New York, NY, for an explanation of codon degeneracy and the genetic code*).

The phrases "isolated" or "biologically pure" refer to material which is substantially or essentially free from components which normally accompany it as found in its native state. Thus, the binding domain polypeptides of this invention do not contain materials normally associated with their *in situ* environment, e.g., other proteins from a merozoite membrane. Typically, isolated proteins of the invention are at least about 80% pure, usually at least about 90%, and preferably at least about 95% as measured by band intensity on a silver stained gel.

Protein purity or homogeneity may be indicated by a number of means well known in the art, such as polyacrylamide gel electrophoresis of a protein sample, followed by visualization upon staining. For certain purposes high resolution will be needed and HPLC or a similar means for purification utilized.

The term "residue" refers to an amino acid (D or L) or amino acid mimetic incorporated in a oligopeptide by an amide bond or amide bond mimetic. An amide bond mimetic of the invention includes peptide backbone modifications well known to those skilled in the art.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 represents an alignment of the predicted amino acid sequences of the DABP binding domain (Vivax) (SEQ ID NO:25), the two homologous SABP domains (SABP F1 (SEQ ID NO:26) and SABP F2 (SEQ ID NO:27)) and the sequenced members of the *DBL* gene family (ebl-1 (SEQ ID NO:28), E31a (SEQ ID NO:29), EBL-2 (SEQ ID NO:30)) and the three homologous Proj3 domains (F1 (SEQ ID NO:31), F2 (SEQ ID NO:32) and F3 (SEQ ID NO:33)).

Figure 2 represents a schematic of the pRE4 cloning vector.

Figure 3 shows primers useful for isolating sequences encoding the conserved motifs of the invention. Primers UNIEBP5 (SEQ ID NO:35) and UNIEBP5A (SEQ ID NO:36) encode the amino acid sequence of SEQ ID NO:34; primers UNIEBP5B (SEQ ID NO:38) and UNIEBP5C (SEQ ID NO:39) encode the amino acid sequence of SEQ ID NO:37; primers UNIEBP3 (SEQ ID NO:41) and UNIEBP3A (SEQ ID NO:42) encode the amino acid sequence of SEQ ID NO:40; and primers UNIEBP3B (SEQ ID NO:44) and UNIEBP3C (SEQ ID NO:45) encode the amino acid sequence of SEQ ID NO:43.

Figure 4 shows the relative position of the E31a ORF on chromosome 7.

Figure 5 shows a map of a *var* gene cluster on chromosome 7. Relative positions of four YACs (PfyEF2, PfyEF6, PfyKF8, PfyED9) are indicated under the chromosome 7 line at the top of the figure. YACs PfyEF6 and PfyKF8 lie entirely within a segment linked to CQR in a genetic cross, whereas YACs PfyED9 and PfyEF2 extend beyond sites (identified by pE53a and pH270.5) that are dissociated from the chloroquine response. The *var* cluster extends over a region of 100-150 kb in PfyED9. Exons and introns of the *var-1*, *var-2* and *var-3* genes within the sequenced 40 kb segment are represented by solid and dotted lines, respectively; arrows show the coding direction. Two more *var* elements outside of the sequenced region, identified by conserved restriction sites and cross-hybridization, are indicated by dashed-lines (*var-2c* and *var-3c*). Bold letters mark repeated restriction sites that suggest a duplication in the *var-2/var-3* and *var-2c/var-3c* segments. Enzyme recognition sites: A, *Apal*; B, *Bgl*; C, *Clal*; D, *HindIII*; E, *HaeIII*; H, *BssHII*; K, *KpnI*; M, *BamHI*; P, *HpaI*; S, *SmaI*. *HindIII* and *HaeIII* sites outside of the sequenced region were not mapped. Positions and sizes of inserts from the Dd2 subsegment library are indicated: a, pE280b; b, pB20.3; c, pB600; d, pE21b; e, pB20.24; f, pE32b; h, pE241a; i, pE240a/51d; j, pE33a; k, pB20.23; l, AL17BA6; m, pB20.26; n, pB20SU.27; o, p15J2J3. Inserts from the PfyED9 34 kb *Apal-SmaI* fragment library: r, pB3; s, p3G11; t, pJVs; u, p2E10; v, pIG3; w, p2E3; x, p2B6; y, pE10; z, pJYr; α , pC5; β , p1A3; γ , p1F6; δ , p3C3; ϵ , pA2; ζ , p2A9; η , p3C4; θ , pJZn; κ , p3D8.

DESCRIPTION OF THE PREFERRED EMBODIMENT

The binding of merozoites and schizonts to erythrocytes is mediated by specific binding proteins on the surface of the merozoite or schizont and is necessary for erythrocyte invasion. In the case of *P. falciparum*, this binding involves specific interaction between sialic acid glycoprotein residues on the erythrocyte and the sialic acid binding protein (SABP) on the surface of the merozoite or schizont. The ability of purified SABP to bind erythrocytes with chemically or enzymatically altered sialic acid residues paralleled the ability of *P. falciparum* to invade these erythrocytes. Furthermore, sialic acid deficient erythrocytes neither bind SABP nor support invasion by *P. falciparum*. The DNA encoding SABP from *P. falciparum* has also been cloned and sequenced.

In *P. vivax*, specific binding to the erythrocytes involves interaction between the Duffy blood group antigen on the erythrocyte and the Duffy antigen binding protein (DABP) on the merozoite. Duffy binding proteins were defined biologically as those soluble proteins that appear in the culture supernatant after the infected erythrocytes release merozoites which bind to human Duffy positive, but not to human Duffy negative erythrocytes. It has been shown that binding of the *P. vivax* DABP protein to Duffy positive erythrocytes is blocked by antisera to the Duffy blood group determinants. Purified Duffy blood group antigens also block the binding to erythrocytes. DABP has also been shown to bind Duffy blood group determinants on Western blots.

Duffy positive blood group determinants on human erythrocytes are essential for invasion of human erythrocytes by *Plasmodium vivax*. Both attachment and reorientation of *P. vivax* merozoites occur equally well on Duffy positive and negative erythrocytes. A junction then forms between the apical end of the merozoite and the Duffy-positive erythrocyte, followed by vacuole formation and entry of the merozoite into the vacuole. Junction formation and merozoite entry into the erythrocyte do not occur on Duffy negative cells, suggesting that the receptor specific for the Duffy determinant is involved in apical junction formation but not initial attachment. The DNA sequences encoding the DABP from *P. vivax* and *P. knowlesi* have been cloned and sequenced.

P. vivax red cell invasion has an absolute requirement for the Duffy blood group antigen. Isolates of *P. falciparum*, however, vary in their dependency on sialic acid for invasion. Certain *P. falciparum* clones have been developed which invade sialic acid deficient erythrocytes at normal rates. This suggests that certain strains of *P. falciparum* can interact with other ligands on the erythrocyte and so may possess multiple erythrocyte binding proteins with differing specificities.

A basis for the present invention is the discovery of the binding domains in both DABP and SABP. Comparison of the predicted protein sequences of DABP and SABP reveals an amino-terminal, cysteine-rich region in both proteins with a high degree of similarity between the two proteins. The amino-terminal, cysteine-rich region of DABP contains about 325 amino acids, whereas the amino-terminal, cysteine-rich region of SABP contains about 616 amino acids. This is due to an apparent duplication of the amino-terminal, cysteine-rich region in the SABP protein. The cysteine residues are conserved between the two regions of SABP and DABP, as are the amino acids surrounding the cysteine residues and a number of aromatic amino acid residues in this region. The amino-terminal cysteine rich region and another cysteine-rich region near the carboxyl-terminus show the most similarity between the DABP and SABP proteins. The region of the amino acid sequence between these two cysteine-rich regions show only limited similarity between DABP and SABP.

Other *P. falciparum* open reading frames and genes with regions that have substantial identity to binding domains of SABP and DABP have been identified. Multiple copies of these sequences exist in the parasite genome, indicating their important activity in host-parasite interactions. A family of these sequences (the *DBL* family) have been cloned from chromosome 7 subsegment libraries that were constructed during genetic studies of the chloroquine resistance locus (Wellems *et. al.*, *PNAS* 88: 3382-3386 (1991)). Certain of these transcripts are known to be from the *var* family of genes that modulate cytoadherence and antigenic variation of *P. falciparum*-infected erythrocytes (*see*, Example 3, below).

Genes of the *P. falciparum var* family encode 200-350 kD variant surface molecules that determine antigenic and adhesive properties of parasitized erythrocytes. The large repertoire of *var* genes (50-150 copies, having sufficient DNA to account for 2-6% of the haploid genome), the dramatic sequence variation among the gene copies, their variable expression in different parasite lines, the ready detection of DNA rearrangements, and the receptor binding features of the encoded extracellular domains all implicate *var* genes as the major determinants of antigenic variation and cytoadherence in *P. falciparum* malaria.

A second class of *DBL*-encoding transcripts includes single-copy genes such as *ebf-1*. Genetic linkage studies have placed this gene within a region of chromosome 13 that affects invasion of malarial parasites in human red blood cells (Wellems *et al.*, *Cell* 49:633-642 (1987)). Both SABP and *ebf-1* show restriction patterns that are well conserved among different parasite isolates. This conservation of gene structure and the sequence relationships between the *ebf-1* and SABP domains suggest that *ebf-1* encodes a novel erythrocyte binding molecule having receptor properties distinct from those of SABP.

Southern hybridization experiments using probes from these open reading frames have indicated that additional copies of these conserved sequences are located elsewhere in the genome. The largest of the open reading frames on chromosome 7 is 8 kilobases and contains four tandem repeats homologous to the N-terminal, cysteine-rich unit of SABP and DABP.

Figure 1 represents an alignment of the DBL family with the DABP binding domain and two homologous regions of SABP (F_1 and F_2). The DBL family is divided into two sub-families to achieve optimal alignment. Conserved cysteine residues are shown in bold face and conserved aromatic residues are underlined.

The polypeptides of the invention can be used to raise monoclonal antibodies specific for the binding domains of SABP, DABP or the conserved regions in the *DBL* gene family. The antibodies can be used for diagnosis of malarial infection or as therapeutic agents to inhibit binding of merozoites to erythrocytes. The production of monoclonal antibodies against a desired antigen is well known to those of skill in the art and is not reviewed in detail here.

The multitude of techniques available to those skilled in the art for production and manipulation of various immunoglobulin molecules can thus be readily applied to inhibit binding. As used herein, the terms "immunoglobulin" and "antibody" refer to a protein consisting of one or more polypeptides substantially encoded by immunoglobulin genes. Immunoglobulins may exist in a variety of forms besides antibodies, including for example, Fv, Fab, and $F(ab)_2$, as well as in single chains. For a general review of immunoglobulin structure and function see, *Fundamental Immunology*, 2d Ed., W.E. Paul ed., Ravens Press, N.Y., (1989).

Antibodies which bind polypeptides of the invention may be produced by a variety of means. The production of non-human monoclonal antibodies, e.g., murine, lagomorpha, equine, etc., is well known and may be accomplished by, for example, immunizing the animal with a preparation containing the polypeptide. Antibody-producing cells obtained from the immunized animals are immortalized and screened, or screened first for the production of antibody which inhibits binding between and merozoites and erythrocytes and then immortalized.

For a discussion of general procedures of monoclonal antibody production see Harlow and Lane, *Antibodies, A Laboratory Manual* Cold Spring Harbor Publications, N.Y. (1988).

Thus, the present invention allows targeting of protective immune responses or monoclonal antibodies to sequences in the binding domains that are conserved between SABP, DABP and encoded regions of the *DBL* family. Identification of the binding regions of these proteins facilitates vaccine development because it allows for a focus of effort upon the functional elements of the large molecules. The particular sequences within the binding regions refine the target to critical regions that have been conserved during evolution, and are thus preferred for use as vaccines against the parasite.

The genes of the *DBL* family (which have not previously been sequenced) can be used as markers to detect the presence of the *P. falciparum* parasite in patients. This can be accomplished by means well known to practitioners in the art using tissue or blood from symptomatic patients in PCR reactions with oligonucleotides complementary to portions of the genes of the *DBL* family. Furthermore, sequencing the *DBL* family provides a means for skilled practitioners to generate defined probes to be used as genetic markers in a variety of applications.

Additionally, the present invention defines a conserved motif present in, but not restricted to other members of the subphylum Apicomplexa which participates in host parasite interaction. This motif can be identified in *Plasmodium* species and other parasitic protozoa by the polymerase chain reaction using the synthetic oligonucleotide primers shown in Figure 3. PCR methods are described in detail below. These primers are designed from regions in the conserved motif showing the highest degree of conservation among DABP, SABP and the *DBL* family. Figure 3 shows these regions and the consensus amino acid sequences derived from them.

A. General Methods

Much of the nomenclature and general laboratory procedures required in this application can be found in Sambrook, *et al.*, *Molecular Cloning A Laboratory Manual*, 2nd Ed., Vol. 1-3, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1989. The manual is hereinafter referred to as "Sambrook, *et al.*, 1989."

The practice of this invention involves the construction of recombinant nucleic acids and the expression of genes in transfected cells. Molecular cloning techniques to achieve these ends are known in the art. A wide variety of cloning and *in vitro* amplification methods suitable for the construction of recombinant nucleic acids are well-known to persons of skill. Examples of these techniques and instructions sufficient to direct persons of skill through many cloning exercises are found in Berger and Kimmel, *Guide to Molecular Cloning Techniques, Methods in Enzymology* volume 152 Academic Press, Inc., San Diego, CA (Berger); and *Current Protocols in Molecular Biology*, F.M. Ausubel *et al.*, eds., Current Protocols, a joint venture between Greene Publishing Associates, Inc. and John Wiley & Sons, Inc., (1994 Supplement) (Ausubel).

Examples of techniques sufficient to direct persons of skill through *in vitro* amplification methods, including the polymerase chain reaction (PCR) the ligase chain reaction (LCR), $Q\beta$ -replicase amplification and other RNA polymerase mediated techniques are found in Berger, Sambrook *et al.*, 1989, and Ausubel, as well as Mullis *et al.*, (1987) U.S. Patent No. 4,683,202; *PCR Protocols A Guide to Methods and Applications* (Innis *et al.* eds), Academic Press Inc., San Diego, CA, 1990) ("Innis"); Arnheim & Levinson (October 1, 1990) *C&EN* 36:47; *The*

Journal Of NIH Research (1991) 3, 81-94; Kwoh *et al.* (1989) *Proc. Natl. Acad. Sci. USA* 86, 1173; Guatelli *et al.* (1990) *Proc. Natl. Acad. Sci. USA* 87, 1874; Lomell *et al.* (1989) *J. Clin. Chem* 35, 1826; Landegren *et al.*, (1988) *Science* 241, 1077-1080; Van Brunt (1990) *Biotechnology* 8, 291-294; Wu and Wallace, (1989) *Gene* 4, 560; and Barringer *et al.* (1990) *Gene* 89, 117. Improved methods of cloning *in vitro* amplified nucleic acids are described in Wallace *et al.*, U.S. Pat. No. 5,426,039.

The culture of cells used in the present invention, including cell lines and cultured cells from tissue or blood samples is well known in the art. Freshney (*Culture of Animal Cells, a Manual of Basic Technique, third ed.*, Wiley-Liss, New York, NY (1994)) and the references cited therein provides a general guide to the culture of cells.

DBL genes are optionally bound by antibodies in one of the embodiments of the present invention. Methods of producing polyclonal and monoclonal antibodies are known to those of skill in the art. *See, e.g.*, Coligan (1991) *Current Protocols in Immunology* Wiley/Greene, NY; and Harlow and Lane (1989) *Antibodies: A Laboratory Manual* Cold Spring Harbor Press, NY; Stites *et al.* (eds.) *Basic and Clinical Immunology* (4th ed.) Lange Medical Publications, Los Altos, CA, and references cited therein; Goding (1986) *Monoclonal Antibodies: Principles and Practice* (2d ed.) Academic Press, New York, NY; and Kohler and Milstein (1975) *Nature* 256: 495-497. Other suitable techniques for antibody preparation include selection of libraries of recombinant antibodies in phage or similar vectors. *See, Huse et al.* (1989) *Science* 246: 1275-1281; and Ward, *et al.* (1989) *Nature* 341: 544-546. Specific Monoclonal and polyclonal antibodies will usually bind with a KD of at least about .1 mM, more usually at least about 1 μ M, and most preferably at least about .1 μ M or better.

20 B. Methods for isolating DNA encoding SABP, DABP and DBL binding regions

The nucleic acid compositions of this invention, whether RNA, cDNA, genomic DNA, or a hybrid of the various combinations, may be isolated from natural sources or may be synthesized *in vitro*. The nucleic acids claimed may be present in transformed or transfected whole cells, in a transformed or transfected cell lysate, or in a partially purified or substantially pure form.

25 Techniques for nucleic acid manipulation of genes encoding the binding domains of the invention, such as subcloning nucleic acid sequences encoding polypeptides into expression vectors, labelling probes, DNA hybridization, and the like are described generally in Sambrook *et al.*, 1989.

Recombinant DNA techniques can be used to produce the binding domain polypeptides. In general, the DNA encoding the SABP and DABP binding domains are first cloned or isolated in a form suitable for ligation into an expression vector. After ligation, the vectors containing the DNA fragments or inserts are introduced into a suitable host cell for expression of the recombinant binding domains. The polypeptides are then isolated from the host cells.

35 There are various methods of isolating the DNA sequences encoding the SABP, DABP and DBL binding domains. Typically, the DNA is isolated from a genomic or cDNA library using labelled oligonucleotide probes specific for sequences in the DNA. Restriction endonuclease digestion of genomic DNA or cDNA containing the appropriate genes can be used to isolate the DNA encoding the binding domains of these proteins. Since the DNA

sequences of the SABP and DABP genes are known, a panel of restriction endonucleases can be constructed to give cleavage of the DNA in the desired regions. After restriction endonuclease digestion, DNA encoding SABP binding domain or DABP binding domain is identified by its ability to hybridize with nucleic acid probes, for example on Southern blots, and these DNA regions are isolated by standard methods familiar to those of skill in the art. See
5 Sambrook, *et al.*, 1989.

The polymerase chain reaction can also be used to prepare DABP, SABP DBL binding domain DNA. Polymerase chain reaction technology (PCR) is used to amplify nucleic acid sequences of the DABP and SABP binding domains directly from mRNA, from cDNA, and from genomic libraries or cDNA libraries. The primers shown in Figure 3 are particularly preferred for this process.

10 Appropriate primers and probes for amplifying the SABP and DABP binding region DNA's are generated from analysis of the DNA sequences. In brief, oligonucleotide primers complementary to the two 3' borders of the DNA region to be amplified are synthesized. The polymerase chain reaction is then carried out using the two primers. See *PCR Protocols: A Guide to Methods and Applications*. (Innis, M, Gelfand, D., Sninsky, J. and White, T., (eds.), Academic Press, San Diego, CA (1990). Primers can be selected to amplify the entire DABP regions or
15 to amplify smaller segments of the DABP and SABP binding domains, as desired.

Oligonucleotides for use as probes are chemically synthesized according to the solid phase phosphoramidite triester method first described by Beaucage, S.L. and Caruthers, M.H., 1981, *Tetrahedron Letts.*, 22(20):1859-1862 using an automated synthesizer, as described in Needham-VanDevanter, D.R., *et al.* 1984, *Nucleic Acids Res.*, 12:6159-6168. Purification of oligonucleotides is by either native acrylamide gel electrophoresis or by
20 anion-exchange HPLC as described in Pearson, J.D. and Regnier, F.E., 1983, *J. Chrom.*, 255:137-149.

The sequence of the synthetic oligonucleotides can be verified using the chemical degradation method of Maxam, A.M. and Gilbert, 1980, in W., Grossman, L. and Moldave, D., eds. Academic Press, New York, NY, *Methods in Enzymology* 65:499-560.

Other methods known to those of skill in the art may also be used to isolate DNA encoding all or part of the SABP or DABP binding domains. See Sambrook, *et al.*, 1989.

C. Expression of DABP, SABP and DBL Binding Domain Polypeptides

Once binding domain DNAs are isolated and cloned, one may express the desired polypeptides in a recombinantly engineered cell such as bacteria, yeast, insect (especially employing baculoviral vectors), and mammalian cells. It is expected that those of skill in the art are knowledgeable in the numerous expression systems available for expression of the DNA encoding the DABP and SABP binding domains. No attempt to describe in detail the various methods known for the expression of proteins in prokaryotes or eukaryotes will be made.

In brief summary, the expression of natural or synthetic nucleic acids encoding binding domains will typically be achieved by operably linking the DNA or cDNA to a promoter (which is either constitutive or inducible), followed by incorporation into an expression vector. The vectors can be suitable for replication and
35 integration in either prokaryotes or eukaryotes. Typical expression vectors contain transcription and translation terminators, initiation sequences, and promoters useful for regulation of the expression of the DNA encoding the

binding domains. To obtain high level expression of a cloned gene, it is desirable to construct expression plasmids which contain, at the minimum, a strong promoter to direct transcription, a ribosome binding site for translational initiation, and a transcription/translation terminator.

1. Expression in Prokaryotes

5 Examples of regulatory regions suitable for this purpose in *E. coli* are the promoter and operator region of the *E. coli* tryptophan biosynthetic pathway as described by Yanofsky, C., 1984, J. Bacteriol., 158:1018-1024 and the leftward promoter of phage lambda (P_L) as described by Herskowitz, I. and Hagen, D., 1980, Ann. Rev. Genet., 14:399-445. The inclusion of selection markers in DNA vectors transformed in *E. coli* is also useful. Examples of such markers include genes specifying resistance to ampicillin, tetracycline, or chloramphenicol. 10 See Sambrook *et al.*, 1989, for details concerning selection markers for use in *E. coli*.

The vector is selected to allow introduction into the appropriate host cell. Bacterial vectors are typically of plasmid or phage origin. Appropriate bacterial cells are infected with phage vector particles or transfected with naked phage vector DNA. If a plasmid vector is used, the bacterial cells are transfected with the plasmid vector DNA.

15 Expression systems for expressing the DABP and SABP binding domains are available using *E. coli*, *Bacillus* sp. (Palva, I *et al.*, 1983, Gene 22:229-235; Mosbach, K. *et al.* Nature, 302:543-545 and *Salmonella*. *E. coli* systems are preferred.

The binding domain polypeptides produced by prokaryote cells may not necessarily fold properly. During purification from *E. coli*, the expressed polypeptides may first be denatured and then renatured. This can be 20 accomplished by solubilizing the bacterially produced proteins in a chaotropic agent such as guanidine HCl and reducing all the cysteine residues with a reducing agent such as beta-mercaptoethanol. The polypeptides are then renatured, either by slow dialysis or by gel filtration. U.S. Patent No. 4,511,503.

Detection of the expressed antigen is achieved by methods known in the art as radioimmunoassays, Western blotting techniques or immunoprecipitation. Purification from *E. coli* can be achieved following procedures 25 described in U.S. Patent No. 4,511,503.

2. Synthesis of SABP, DABP and DBL Binding Domains in Eukaryotes

A variety of eukaryotic expression systems such as yeast, insect cell lines and mammalian cells, are known to those of skill in the art. As explained briefly below, the DABP and SABP binding domains may also be expressed in these eukaryotic systems.

30 a. Expression in Yeast

Synthesis of heterologous proteins in yeast is well known and described. *Methods in Yeast Genetics*, Sherman, F., *et al.*, Cold Spring Harbor Laboratory, (1982) is a well recognized work describing the various methods available to produce the binding domains in yeast.

35 Examples of promoters for use in yeast include GAL1,10 (Johnson, M., and Davies, R.W., 1984, Mol. and Cell. Biol., 4:1440-1448) ADH2 (Russell, D., *et al.* 1983, J. Biol. Chem., 258:2674-2682), PH05 (EMBO J. 6:675-680, 1982), and MF α 1 (Herskowitz, I. and Oshima, Y., 1982, in The Molecular Biology of the Yeast

Saccharomyces, (eds. Strathern, J.N. Jones, E.W., and Broach, J.R., Cold Spring Harbor Lab., Cold Spring Harbor, N.Y., pp. 181-209. A multicopy plasmid with a selective marker such as Leu-2, URA-3, Trp-1, and His-3 is also desirable.

5 A number of yeast expression plasmids like YEp6, YEp13, YEp4 can be used as vectors. A gene of interest can be fused to any of the promoters in various yeast vectors. The above-mentioned plasmids have been fully described in the literature (Botstein, *et al.*, 1979, *Gene*, 8:17-24; Broach, *et al.*, 1979, *Gene*, 8:121-133).

10 Two procedures are used in transforming yeast cells. In one case, yeast cells are first converted into protoplasts using zymolyase, lyticase or glucylase, followed by addition of DNA and polyethylene glycol (PEG). The PEG-treated protoplasts are then regenerated in a 3% agar medium under selective conditions. Details of this procedure are given in the papers by J.D. Beggs, 1978, *Nature* (London), 275:104-109; and Hinnen, A., *et al.*, 1978, *Proc. Natl. Acad. Sci. USA*, 75:1929-1933. The second procedure does not involve removal of the cell wall. Instead the cells are treated with lithium chloride or acetate and PEG and put on selective plates (Ito, H., *et al.*, 1983, *J. Bact.*, 153:163-168).

15 The binding domains can be isolated from yeast by lysing the cells and applying standard protein isolation techniques to the lysates. The monitoring of the purification process can be accomplished by using Western blot techniques or radioimmunoassays of other standard immunoassay techniques.

b. Expression in Mammalian and Insect Cell Cultures

20 Illustrative of cell cultures useful for the production of the binding domains are cells of insect or mammalian origin. Mammalian cell systems often will be in the form of monolayers of cells although mammalian cell suspensions may also be used. Illustrative examples of mammalian cell lines include VERO and HeLa cells, Chinese hamster ovary (CHO) cell lines, W138, BHK, Cos-7 or MDCK cell lines.

25 As indicated above, the vector, *e. g.*, a plasmid, which is used to transform the host cell, preferably contains DNA sequences to initiate transcription and sequences to control the translation of the antigen gene sequence. These sequences are referred to as expression control sequences. When the host cell is of insect or mammalian origin illustrative expression control sequences are obtained from the SV-40 promoter (*Science*, 222:524-527, 1983), the CMV I.E. Promoter (*Proc. Natl. Acad. Sci.* 81:659-663, 1984) or the metallothionein promoter (*Nature* 296:39-42, 1982). The cloning vector containing the expression control sequences is cleaved using restriction enzymes and adjusted in size as necessary or desirable and ligated with DNA coding for the SABP or DABP polypeptides by means well known in the art.

30 As with yeast, when higher animal host cells are employed, polyadenylation or transcription terminator sequences from known mammalian genes need to be incorporated into the vector. An example of a terminator sequence is the polyadenylation sequence from the bovine growth hormone gene. Sequences for accurate splicing of the transcript may also be included. An example of a splicing sequence is the VPI intron from SV40 (Sprague, J. *et al.*, 1983, *J. Virol.* 45: 773-781).

35 Additionally, gene sequences to control replication in the host cell may be incorporated into the vector such as those found in bovine papilloma virus type-vectors. Saveria-Campo, M., 1985, "Bovine Papilloma virus

DNA a Eukaryotic Cloning Vector" in DNA Cloning Vol. II a Practical Approach Ed. D.M. Glover, IRL Press, Arlington, Virginia pp. 213-238.

The host cells are competent or rendered competent for transformation by various means. There are several well-known methods of introducing DNA into animal cells. These include: calcium phosphate precipitation, fusion of the recipient cells with bacterial protoplasts containing the DNA, treatment of the recipient cells with liposomes containing the DNA, DEAE dextran, electroporation and micro-injection of the DNA directly into the cells.

The transformed cells are cultured by means well known in the art. Biochemical Methods in Cell Culture and Virology, Kuchler, R.J., Dowden, Hutchinson and Ross, Inc., (1977). The expressed DABP and SABP binding domain polypeptides are isolated from cells grown as suspensions or as monolayers. The latter are recovered by well known mechanical, chemical or enzymatic means.

c. Expression in recombinant vaccinia virus- or adenovirus-infected cells

In addition to use in recombinant expression systems, the isolated binding domain DNA sequences can also be used to transform viruses that transfect host cells in the patient. Live attenuated viruses, such as vaccinia or adenovirus, are convenient alternatives for vaccines because they are inexpensive to produce and are easily transported and administered. Vaccinia vectors and methods useful in immunization protocols are described, for example, in U.S. Patent No. 4,722,848.

Suitable viruses for use in the present invention include, but are not limited to, pox viruses, such as canarypox and cowpox viruses, and vaccinia viruses, alpha viruses, adenoviruses, and other animal viruses. The recombinant viruses can be produced by methods well known in the art, for example, using homologous recombination or ligating two plasmids. A recombinant canarypox or cowpox virus can be made, for example, by inserting the DNA's encoding the DABP and SABP binding domain polypeptides into plasmids so that they are flanked by viral sequences on both sides. The DNA's encoding the binding domains are then inserted into the virus genome through homologous recombination.

A recombinant adenovirus can be produced, for example, by ligating together two plasmids each containing about 50% of the viral sequence and the DNA sequence encoding erythrocyte binding domain polypeptide. Recombinant RNA viruses such as the alpha virus can be made via a cDNA intermediate using methods known in the art.

In the case of vaccinia virus (for example, strain WR), the DNA sequence encoding the binding domains can be inserted in the genome by a number of methods including homologous recombination using a transfer vector, pTKgpt-DFIS as described in Kaslow, *et al.*, *Science* 252:1310-1313 (1991).

Alternately the DNA encoding the SABP and DABP binding domains may be inserted into another plasmid designed for producing recombinant vaccinia, such as pGS62, Langford, C.L., *et al.*, 1986, *Mol. Cell. Biol.* 6:3191-3199. This plasmid consists of a cloning site for insertion of foreign genes, the P7.5 promoter of vaccinia to direct synthesis of the inserted gene, and the vaccinia TK gene flanking both ends of the foreign gene.

Confirmation of production of recombinant virus can be achieved by DNA hybridization using cDNA encoding the DABP and SABP binding domain polypeptides and by immunodetection techniques using antibodies

specific for the expressed binding domain polypeptides. Virus stocks may be prepared by infection of cells such as HELA S3 spinner cells and harvesting of virus progeny.

5 The recombinant virus of the present invention can be used to induce anti-SABP and anti-DABP binding domain antibodies in mammals, such as mice or humans. In addition, the recombinant virus can be used to produce the SABP and DABP binding domains by infecting host cells *in vitro*, which in turn express the polypeptide (see section on expression of SABP and DABP binding domains in eukaryotic cells, above).

10 The present invention also relates to host cells infected with the recombinant virus. The host cells of the present invention are preferably mammalian, such as BSC-1 cells. Host cells infected with the recombinant virus express the DABP and SABP binding domains on their cell surfaces. In addition, membrane extracts of the infected cells induce protective antibodies when used to inoculate or boost previously inoculated mammals.

D. Purification of the SABP, DABP and DBL Binding Domain Polypeptides

15 The binding domain polypeptides produced by recombinant DNA technology may be purified by standard techniques well known to those of skill in the art. Recombinantly produced binding domain polypeptides can be directly expressed or expressed as a fusion protein. The protein is then purified by a combination of cell lysis (*e. g.*, sonication) and affinity chromatography. For fusion products, subsequent digestion of the fusion protein with an appropriate proteolytic enzyme release the desired SABP and DABP binding domains.

20 The polypeptides of this invention may be purified to substantial purity by standard techniques well known in the art, including selective precipitation with such substances as ammonium sulfate, column chromatography, immunopurification methods, and others. See, for instance, R. Scopes, *Protein Purification: Principles and Practice*, Springer-Verlag, New York, NY (1982).

E. Production of Binding Domains by protein chemistry techniques

25 The polypeptides of the invention can be synthetically prepared in a wide variety of ways. For instance polypeptides of relatively short size, can be synthesized in solution or on a solid support in accordance with conventional techniques. Various automatic synthesizers are commercially available and can be used in accordance with known protocols. See, for example, Stewart and Young, *Solid Phase Peptide Synthesis*, 2d. ed., Pierce Chemical Co. (1984).

30 Alternatively, purified and isolated SABP, DABP or DBL family proteins may be treated with proteolytic enzymes in order to produce the binding domain polypeptides. For example, recombinant DABP and SABP proteins may be used for this purpose. The DABP and SABP protein sequence may then be analyzed to select proteolytic enzymes to be used to generate polypeptides containing desired regions of the DABP and SABP binding domain. The desired polypeptides are then purified by using standard techniques for protein and peptide purification. For a review of standard techniques see, *Methods in Enzymology*, "Guide to Protein Purification", M. Deutscher, ed. Vol. 182 (1990), pages 619-626.

F. Modification of nucleic acid and polypeptide sequences

35 The nucleotide sequences used to transfect the host cells used for production of recombinant binding domain polypeptides can be modified according to standard techniques to yield binding domain polypeptides,

with a variety of desired properties. The binding domain polypeptides of the present invention can be readily designed and manufactured utilizing various recombinant DNA techniques well known to those skilled in the art. For example, the binding domain polypeptides can vary from the naturally-occurring sequence at the primary structure level by amino acid insertions, substitutions, deletions, and the like. These modifications can be used in a number of combinations to produce the final modified protein chain.

The amino acid sequence variants can be prepared with various objectives in mind, including facilitating purification and preparation of the recombinant polypeptides. The modified polypeptides are also useful for modifying plasma half-life, improving therapeutic efficacy, and lessening the severity or occurrence of side effects during therapeutic use. The amino acid sequence variants are usually predetermined variants not found in nature but exhibit the same immunogenic activity as naturally occurring polypeptides. For instance, polypeptide fragments comprising only a portion (usually at least about 60-80%, typically 90-95%) of the primary structure may be produced. For use as vaccines, polypeptide fragments are typically preferred so long as at least one epitope capable of eliciting production of blocking antibodies remains.

In general, modifications of the sequences encoding the binding domain polypeptides may be readily accomplished by a variety of well-known techniques, such as site-directed mutagenesis (see, Gilman and Smith, *Gene* 8:81-97 (1979) and Roberts, S. *et al.*, *Nature* 328:731-734 (1987)). One of ordinary skill will appreciate that the effect of many mutations is difficult to predict. Thus, most modifications are evaluated by routine screening in a suitable assay for the desired characteristic. For instance, changes in the immunological character of the polypeptide can be detected by an appropriate competitive binding assay. Modifications of other properties such as redox or thermal stability, hydrophobicity, susceptibility to proteolysis, or the tendency to aggregate are all assayed according to standard techniques.

G. Diagnostic and Screening Assays

The polypeptides and nucleic acids of the invention can be used in diagnostic applications for the detection of merozoites or nucleic acids in a biological sample. The presence of parasites can be detected using several well recognized specific binding assays based on immunological results. (See U.S. Patents 4,366,241; 4,376,110; 4,517,288; and 4,837,168). For instance, labeled monoclonal antibodies to polypeptides of the invention can be used to detect merozoites in a biological sample. Alternatively, labelled polypeptides of the invention can be used to detect the presence of antibodies to SABP or DABP in a biological sample. For a review of the general procedures in diagnostic immunoassays, see also *Basic and Clinical Immunology* 7th Edition (D. Stites and A. Terr ed.) 1991.

In addition, modified polypeptides, antibodies or other compounds capable of inhibiting the interaction between SABP or DABP and erythrocytes can be assayed for biological activity. For instance, polypeptides can be recombinantly expressed on the surface of cells and the ability of the cells to bind erythrocytes can be measured as described below. Alternatively, peptides or antibodies can be tested for the ability to inhibit binding between erythrocytes and merozoites or SABP and DABP.

Cell-free assays can also be used to measure binding of DABP or SABP polypeptides to isolated Duffy antigen or glycophorin polypeptides. For instance, the erythrocyte proteins can be immobilized on a solid surface and binding of labelled SABP or DABP polypeptides can be measured.

Many assay formats employ labelled assay components. The labelling systems can be in a variety of forms. 5. The label may be coupled directly or indirectly to the desired component of the assay according to methods well known in the art. A wide variety of labels may be used. The component may be labelled by any one of several methods. The most common method of detection is the use of autoradiography with ^3H , ^{125}I , ^{35}S , ^{14}C , or ^{32}P labelled compounds or the like. Non-radioactive labels include ligands which bind to labelled antibodies, fluorophores, chemiluminescent agents, enzymes, and antibodies which can serve as specific binding pair members for a labelled 10 ligand. The choice of label depends on sensitivity required, ease of conjugation with the compound, stability requirements, and available instrumentation.

In addition, the polypeptides of the invention can be assayed using animal models, well known to those of skill in the art. For *P. falciparum* the *in vivo* models include *Aotus sp.* monkeys or chimpanzees; for *P. vivax* the *in vivo* models include *Saimiri* monkeys.

15 In the case of the use nucleic acids for diagnostic purposes, standard nucleic hybridization techniques can be used to detect the presence of the genes identified here (*e.g.*, members of the *DBL* family). If desired, nucleic acids in the sample may first be amplified using standard procedures such as PCR. Diagnostic kits comprising the appropriate primers and probes can also be prepared.

H. DBL Targeted Therapeutics

20 *DBL* polypeptides are expressed on the surface of *Plasmodium*-infected erythrocytes. As such, they present ideal targets for therapeutics which target infected erythrocytes. In one preferred embodiment of the present invention, cytotoxic antibodies or antibody fusion proteins with cytotoxic agents are targeted against *DBL* proteins, killing infected erythrocytes and inhibiting the reproduction of *Plasmodium* in an infected host.

The procedure for attaching a cytotoxic agent to an antibody will vary according to the chemical 25 structure of the agent. Antibodies and cytotoxic agents are typically bound together chemically or, where the antibody and cytotoxic agents are both polypeptides, are optionally synthesized recombinantly as a fusion protein. Polypeptides typically contain variety of functional groups; *e.g.*, carboxylic acid (COOH) or free amine ($-\text{NH}_2$) groups, which are available for reaction with a suitable functional group on either the antibody or the cytotoxic agent.

Alternatively, antibodies or cytotoxic agents are derivitized to attach additional reactive functional 30 groups. The derivatization optionally involves attachment of linker molecules such as those available from Pierce Chemical Company, Rockford Illinois. A "linker", as used herein, is a molecule that is used to join the nucleic acid binding molecule to the receptor ligand. The linker is capable of forming covalent bonds to both the antibody and the cytotoxic agent. Suitable linkers are well known to those of skill in the art and include, but are not limited to, straight or branched-chain carbon linkers, heterocyclic carbon linkers, or peptide linkers. Where the antibody and the 35 cytotoxic agent are polypeptides, the linkers are joined to the constituent amino acids through their side groups (*e.g.*, through a disulfide linkage to cysteine) or to the alpha carbon amino and carboxyl groups of the terminal amino acids.

A bifunctional linker having one functional group reactive with a group on a particular ligand, and another group reactive with a nucleic acid binding molecule, can be used to form the desired conjugate. Alternatively, derivatization can proceed through chemical treatment of the ligand or nucleic acid binding molecule, *e.g.*, glycol cleavage of the sugar moiety of a glycoprotein with periodate to generate free aldehyde groups. The free aldehyde groups on the glycoprotein may be reacted with free amine or hydrazine groups on an agent to bind the agent thereto (See, *e.g.*, U.S. Patent No. 4,671,958). Procedures for generation of free sulfhydryl groups on polypeptides, are known (See, *e.g.*, U.S. Pat. No. 4,659,839).

Many procedures and linker molecules for attachment of various compounds to proteins are known. See, for example, European Patent Application No. 188,256; U.S. Patent Nos. 4,671,958, 4,659,839, 4,414,148, 4,699,784; 4,680,338; 4,569,789; and 4,589,071; and Borlinghaus *et al.* *Cancer Res.* 47: 4071-4075 (1987). In particular, production of various antibody conjugates is well-known within the art and can be found, for example in Thorpe *et al.*, *Monoclonal Antibodies in Clinical Medicine*, Academic Press, pp. 168-190 (1982), Waldmann, *Science*, 252: 1657 (1991), and U.S. Patent Nos. 4,545,985 and 4,894,443.

A number of antibodies which bind cell surface receptors have been converted to form suitable for incorporation into fusion proteins, and similar strategies are used to create fusion-protein antibodies which bind DBR polypeptides. see Batra *et al.*, *Mol. Cell. Biol.*, 11: 2200-2205 (1991); Batra *et al.*, *Proc. Natl. Acad. Sci. USA*, 89: 5867-5871 (1992); Brinkmann, *et al. Proc. Natl. Acad. Sci. USA*, 88: 8616-8620 (1991); Brinkmann *et al.*, *Proc. Natl. Acad. Sci. USA*, 90: 547-551 (1993); Chaudhary *et al.*, *Proc. Natl. Acad. Sci. USA*, 87: 1066-1070 (1990); Friedman *et al.*, *Cancer Res.* 53: 334-339 (1993); Kreitman *et al.*, *J. Immunol.*, 149: 2810-2815 (1992); Nicholls *et al.*, *J. Biol. Chem.*, 268: 5302-5308 (1993); and Wells, *et al.*, *Cancer Res.*, 52: 6310-6317 (1992), respectively).

B. Production of Fusion Proteins

Where the antibody fragment and/or the cytotoxic agents are relatively short polypeptides (*i.e.*, less than about 50 amino acids) they are often synthesized using standard chemical peptide synthesis techniques. Where both molecules are relatively short, a chimeric molecule is optionally synthesized as a single contiguous polypeptide. Alternatively, the ligand and the nucleic acid binding molecule can be synthesized separately and then fused chemically.

Solid phase synthesis in which the C-terminal amino acid of the sequence is attached to an insoluble support followed by sequential addition of the remaining amino acids in the sequence is a preferred method for the chemical synthesis of the ligands of this invention. Techniques for solid phase synthesis are described by Barany and Merrifield, *Solid-Phase Peptide Synthesis*; pp. 3-284 in *The Peptides: Analysis, Synthesis, Biology. Vol. 2: Special Methods in Peptide Synthesis, Part A.*, Merrifield, *et al.*, *J. Am. Chem. Soc.*, 85: 2149-2156 (1963), and Stewart *et al.*, *Solid Phase Peptide Synthesis, 2nd ed.* Pierce Chem. Co., Rockford, Ill. (1984).

In a preferred embodiment, the fusion molecules of the invention are synthesized using recombinant nucleic acid methodology. Generally this involves creating a nucleic acid sequence that encodes the receptor-targeted fusion molecule, placing the nucleic acid in an expression cassette under the control of a particular promoter, expressing the protein in a host, isolating the expressed protein and, if required, renaturing the protein. Techniques

sufficient to guide one of skill through such procedures are found in, *e.g.*, Berger, Sambrook, Ausubel, Innis, and Freshney (all *supra*).

While the two molecules are often joined directly together, one of skill will appreciate that the molecules may be separated by a peptide spacer consisting of one or more amino acids. Generally the spacer will have no specific biological activity other than to join the proteins or to preserve some minimum distance or other spatial relationship between them. However, the constituent amino acids of the spacer may be selected to influence some property of the molecule such as the folding, net charge, or hydrophobicity.

Once expressed, recombinant fusion proteins can be purified according to standard procedures, including ammonium sulfate precipitation, affinity columns, column chromatography, gel electrophoresis and the like (see, generally, R. Scopes, *Protein Purification*, Springer-Verlag, N.Y. (1982), Deutscher, *Methods in Enzymology Vol. 182: Guide to Protein Purification.*, Academic Press, Inc. N.Y. (1990)). Substantially pure compositions of about 50 to 95% homogeneity are preferred, and 80 to 95% or greater homogeneity are most preferred for use as therapeutic agents.

One of skill in the art will recognize that after chemical synthesis, biological expression, or purification, the fusion molecule may possess a conformation substantially different than the native conformations of the constituent polypeptides. In this case, it is often necessary to denature and reduce the polypeptide and then to cause the polypeptide to re-fold into the preferred conformation. Methods of reducing and denaturing proteins and inducing re-folding are well known to those of skill in the art (See, Debinski *et al. J. Biol. Chem.*, 268: 14065-14070 (1993); Kreitman and Pastan, *Bioconjug. Chem.*, 4: 581-585 (1993); and Buchner, *et al., Anal. Biochem.*, 205: 263-270 (1992).

I. Pharmaceutical compositions comprising binding domain polypeptides

The polypeptides of the invention are useful in therapeutic and prophylactic applications for the treatment of malaria. Pharmaceutical compositions of the invention are suitable for use in a variety of drug delivery systems. Suitable formulations for use in the present invention are found in *Remington's Pharmaceutical Sciences*, Mack Publishing Company, Philadelphia, PA, 17th ed. (1985). For a brief review of methods for drug delivery, see, Langer, *Science* 249:1 527-1533 (1990).

The polypeptides of the present invention can be used in pharmaceutical and vaccine compositions that are useful for administration to mammals, particularly humans. The polypeptides can be administered together in certain circumstances, *e.g.* where infection by both *P. falciparum* and *P. vivax* is likely. Thus, a single pharmaceutical composition can be used for the treatment or prophylaxis of malaria caused by both parasites.

The compositions are suitable for single administrations or a series of administrations. When given as a series, inoculations subsequent to the initial administration are given to boost the immune response and are typically referred to as booster inoculations.

The pharmaceutical compositions of the invention are intended for parenteral, topical, oral or local administration. Preferably, the pharmaceutical compositions are administered parenterally, *e.g.*, intravenously, subcutaneously, intradermally, or intramuscularly. Thus, the invention provides compositions for parenteral

administration that comprise a solution of the agents described above dissolved or suspended in an acceptable carrier, preferably an aqueous carrier. A variety of aqueous carriers may be used, *e.g.*, water, buffered water, 0.4% saline, 0.3% glycine, hyaluronic acid and the like. These compositions may be sterilized by conventional, well known sterilization techniques, or may be sterile filtered. The resulting aqueous solutions may be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile solution prior to administration. The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions, such as pH adjusting and buffering agents, tonicity adjusting agents, wetting agents and the like, for example, sodium acetate, sodium lactate, sodium chloride, potassium chloride, calcium chloride, sorbitan monolaurate, triethanolamine oleate, etc.

For solid compositions, conventional nontoxic solid carriers may be used which include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium carbonate, and the like. For oral administration, a pharmaceutically acceptable nontoxic composition is formed by incorporating any of the normally employed excipients, such as those carriers previously listed, and generally 10-95% of active ingredient and more preferably at a concentration of 25%-75%.

For aerosol administration, the polypeptides are preferably supplied in finely divided form along with a surfactant and propellant. The surfactant must, of course, be nontoxic, and preferably soluble in the propellant. Representative of such agents are the esters or partial esters of fatty acids containing from 6 to 22 carbon atoms, such as caproic, octanoic, lauric, palmitic, stearic, linoleic, linolenic, olesteric and oleic acids with an aliphatic polyhydric alcohol or its cyclic anhydride. Mixed esters, such as mixed or natural glycerides may be employed. A carrier can also be included, as desired, as with, *e.g.*, lecithin for intranasal delivery.

In certain embodiments patients with malaria may be treated with SABP or DABP polypeptides or other specific blocking agents (*e.g.* monoclonal antibodies) that prevent binding of *Plasmodium* merozoites and schizonts to the erythrocyte surface.

The amount administered to the patient will vary depending upon what is being administered, the state of the patient and the manner of administration. In therapeutic applications, compositions are administered to a patient already suffering from malaria in an amount sufficient to inhibit spread of the parasite through erythrocytes and thus cure or at least partially arrest the symptoms of the disease and its complications. An amount adequate to accomplish this is defined as "therapeutically effective dose." Amounts effective for this use will depend on the severity of the disease, the particular composition, and the weight and general state of the patient. Generally, the dose will be in the range of about 1mg to about 5gm per day, preferably about 100 mg per day, for a 70 kg patient.

Alternatively, the polypeptides of the invention can be used prophylactically as vaccines. The vaccines of the invention contain as an active ingredient an immunogenically effective amount of the binding domain polypeptide or of a recombinant virus as described herein. The immune response may include the generation of antibodies; activation of cytotoxic T lymphocytes (CTL) against cells presenting peptides derived from the peptides encoded by the SABP, DABP or DBL sequences of the present invention, or other mechanisms well known in the art.

See e.g. Paul *Fundamental Immunology, Second Edition* (Raven Press, New York, NY) for a description of immune response. Useful carriers are well known in the art, and include, for example, thyroglobulin, albumins such as human serum albumin, tetanus toxoid, polyamino acids such as poly(D-lysine:D-glutamic acid), influenza, hepatitis B virus core protein, hepatitis B virus recombinant vaccine. The vaccines can also contain a physiologically tolerable (acceptable) diluent such as water, phosphate buffered saline, or saline, and further typically include an adjuvant. Adjuvants such as incomplete Freund's adjuvant, aluminum phosphate, aluminum hydroxide, or alum are materials well known in the art.

The DNA or RNA encoding the SABP or DABP binding domains and the DBL gene family motifs may be introduced into patients to obtain an immune response to the polypeptides which the nucleic acid encodes. Wolff et. al., *Science* 247: 1465-1468 (1990) which describes the use of nucleic acids to produce expression of the genes which the nucleic acids encode.

Vaccine compositions containing the polypeptides, nucleic acids or viruses of the invention are administered to a patient to elicit a protective immune response against the polypeptide. A "protective immune response" is one which prevents or inhibits the spread of the parasite through erythrocytes and thus at least partially prevent the symptoms of the disease and its complications. An amount sufficient to accomplish this is defined as an "immunogenically effective dose." Amounts effective for this use will depend on the composition, the manner of administration, the weight and general state of health of the patient, and the judgment of the prescribing physician. For peptide compositions, the general range for the initial immunization (that is for therapeutic or prophylactic administration) is from about 100 μ g to about 1 gm of peptide for a 70 kg patient, followed by boosting dosages of from about 100 μ g to about 1 gm of the polypeptide pursuant to a boosting regimen over weeks to months depending upon the patient's response and condition e.g. by measuring levels of parasite in the patient's blood. For nucleic acids, typically 30-1000ug of nucleic acid is injected into a 70kg patient, more typically about 50-150ug of nucleic acid is injected into a 70kg patient followed by boosting doses as appropriate.

The following examples illustrate preferred embodiments of the invention.

EXAMPLE 1: Identification of the amino-terminal, cysteine-rich region of SABP and DABP as binding domains for erythrocytes

1. Expression of the SABP binding domain polypeptide on the surface of Cos cells.

To demonstrate that the amino-terminal, cysteine-rich region of the SABP protein is the sialic acid binding region, this region of the protein was expressed on the surface of mammalian Cos cells *in vitro*. This DNA sequence is from position 1 to position 1848 of the SABP DNA sequence (SEQ ID No 3). Polymerase chain reaction technology (PCR) was used to amplify this region of the SABP DNA directly from the cloned gene.

Sequences corresponding to restriction endonuclease sites for PvuII or ApaI were incorporated into the oligonucleotide sequence of the probes used in PCR amplification in order to facilitate insertion of the PCR-amplified regions into the pRE4 vector (see below). The specific oligonucleotides, 5'-ATCGATCAGCTGGGAAGAAATACTTCATCT-3'(SEQID NO:17) and 5'-ATCGATGGGCCCCGAAGTTTGTTTCATTATT-3'

(SEQ ID NO:18) were synthesized. These oligonucleotides were used as primers to PCR-amplify the region of the DNA sequence encoding the cysteine-rich amino terminal region of the SABP protein.

PCR conditions were based on the standard described in Saiki, *et al.*, *Science* 239: 487-491 (1988). Template DNA was provided from cloned fragments of the gene encoding SABP which had been spliced and re-cloned as a single open-reading frame piece.

The vector, pRE4, used for expression in Cos cells is shown in Figure 2. The vector has an SV40 origin of replication, an ampicillin resistance marker and the Herpes simplex virus glycoprotein D gene (HSV glyD) cloned downstream of the Rous sarcoma virus long terminal repeats (RSV LTR). Part of the extracellular domain of the HSV glyD gene was excised using the PvuII and ApaI sites in HSV glyD.

As described above, the PCR oligonucleotide primers contained the PvuII or ApaI restriction sites. The PCR-amplified DNA fragments obtained above were digested with the restriction enzymes PvuII and ApaI and cloned into the PvuII and ApaI sites of the vector pRE4. These constructs were designed to express regions of the SABP protein as chimeric proteins with the signal sequence of HSV glyD at the N-terminal end and the transmembrane and cytoplasmic domain of HSV glyD at the C-terminal end. The signal sequence of HSV glyD targets these chimeric proteins to the surface of Cos cells and the transmembrane segment of HSV glyD anchors these chimeric proteins to the Cos cell surface.

Mammalian Cos cells were transfected with the pRE4 constructs containing the PCR-amplified SABP DNA regions, by calcium phosphate precipitation according to standard techniques.

2. Expression of the DABP binding domain polypeptide on the surface of Cos cells.

To demonstrate that the amino-terminal, cysteine-rich region of the DABP protein is the binding domain, this region was expressed on the surface of Cos cells. This region of the DNA sequence from position 1-975 was first PCR-amplified (SEQ ID No 1).

Sequences corresponding to restriction endonuclease sites for PvuII or ApaI were incorporated into the oligonucleotide probes used for PCR amplification in order to facilitate subsequent insertion of the amplified DNA into the pRE4 vector, as described above. The oligonucleotides, 5'-TCTCGTCAGCTGACGATCTCTAGTGCTATT-3' (SEQ ID NO:19) and 5'-ACGAGTGGGCCCTGTCACAACCTCCTGAGT-3' (SEQ ID NO:20) were synthesized. These oligonucleotides were used as primers to amplify the region of the DABP DNA sequence encoding the cysteine-rich, amino-terminal region of the DABP protein directly from the cloned DABP gene, using the same conditions described above.

The same pRE4 vector described above in the section on expression of SABP regions in Cos cells was also used as a vector for the DABP DNA regions.

3. Binding studies with erythrocytes.

To demonstrate their ability to bind human erythrocytes, the transfected Cos cells expressing binding domains from DABP and SABP were incubated with erythrocytes for two hours at 37°C in culture media (DMEM/10% FBS). The non-adherent erythrocytes were removed with five washes of phosphate-buffered saline and the bound erythrocytes were observed by light microscopy. Cos cells expressing the amino terminal, cysteine-rich

SABP polypeptides on their surface bound untreated human erythrocytes, but did not bind neuraminidase treated erythrocytes, that is, erythrocytes which lack sialic acid residues on their surface. Cos cells expressing other regions of the SABP protein on their surface did not bind human erythrocytes. These results identified the amino-terminal, cysteine-rich region of SABP as the erythrocyte binding domain and indicated that the binding of Cos cells expressing these regions to human erythrocytes is specific. Furthermore, the binding of the expressed region to erythrocytes is identical to the binding pattern seen for the authentic SABP-175 molecule upon binding to erythrocytes.

Similarly, Cos cells expressing the amino-terminal cysteine-rich region of DABP on their surface bound Duffy-positive human erythrocytes, but did not bind Duffy-negative human erythrocytes, that is erythrocytes which lack the Duffy blood group antigen. Cos cells expressing other regions of the DABP protein on their surface did not bind human erythrocytes. These results identified the amino-terminal cysteine rich region of DABP as the erythrocyte binding domain and indicated that the binding of the Cos cells was specific.

EXAMPLE 2: Isolation of polynucleotide sequences in the DBL family

P. falciparum clones and cell line used include the following. *P. falciparum* clones 3D7, D10, LF4/1, Camp/A1, SL/D6, HB3, 7G8, V1/S, T2/C6, KMWII, ItG2F6, FCR3/A2 and Dd2 have been previously tabulated (Dolan, *et al.* (1993), *Mol. Biochem. Parasitol.* 61, 137-142). Line Dd2/NM1 was selected from clone Dd2 for invasion via a sialic acid-independent pathway (Dolan, *et al.* (1990), *J. Clin. Invest.* 86, 618-624). All parasites were maintained *in vitro* by standard methods (Trager, *et al.* (1976), *Science* 193, 673-675).

DNA and RNA Isolation and Analysis. DNA was extracted as described (Peterson, *et al.* (1990), *Proc. Natl. Acad. Sci. USA* 87, 3018-3022). Endonuclease digestion, agarose gel electrophoresis, and filter hybridizations were performed by standard methods (Sambrook, *et al.*, 1989). All hybridizations were at 56°C (Sambrook, *et al.*, 1989). Blots were washed for 2 min. at room temperature in 2x standard saline/phosphate/EDTA (SSPE) with 0.5% SDS, followed by two higher stringency washes at 50°C in 0.3xSSPE with 0.5% SDS. Parasite chromosomes were embedded in agarose blocks and separated by pulsed field gel electrophoresis (Dolan, *et al.* (1993), *Methods. Mol. Biol.* 21, 319-332). RNA was isolated from cultured parasites by LiCl extraction of Catrimox-14-precipitated RNA (Dahle, *et al.* (1993), *BioTechniques* 15, 1102-1105). Agarose gel electrophoresis of total RNA and filter hybridizations were performed by standard methods (Sambrook, *et al.*, (1989).

Oligonucleotide Primers and PCR. Primers specific for E31a used in a RT-PCR to test for expression of this sequence were E31aT2 (5'-AGA-CCT-CAA-TTT-CTA-AG-3') (SEQ ID NO:21) and E31aRev1 (5'-AAT-CGC-GAG-CAT-CAT-CTG-3') (SEQ ID NO:22).

Two primers were used to amplify additional sequences from genes encoding *DBL* domains. These were designed from conserved amino acids encoded in the *DBL* domain of the eba-175 and E31a sequences. After adaptation to incorporate the most frequently-used *P. falciparum* codons, forward primer UNIEBP5' [5'-CC(A/G)-AG(G/A)-AG(G/A)-CAA-(G/A)AA-(C/T)TA-TG-3'] (SEQ ID NO:23), based upon the amino acid sequence PRRQKLC, and reverse primer UNIEBP3' [5'-CCA-(A/T)C(T/G)-(T/G)A(A/G)-(A/G)AA-TTG-(A/T)GG-3'] (SEQ ID NO:24), based upon the amino acid sequence PQFLRW, were synthesized.

RT-PCR amplifications were performed as described (Kawasaki, *et al.* (1990), *PCR Protocols, A Guide to Methods and Applications*, eds. Innis, M.A., Gelfand, D.H., Sninsky, J.J. & White, T.J. (Academic, San Diego), pp. 21-27). In brief, 0.5 to 1 mg of total RNA was treated with RQ1 DNase (Promega), phenol/chloroform extracted, and ethanol precipitated. The RNA was then annealed with random oligonucleotide primers and extended with Superscript reverse transcriptase (GIBCO/BRL). PCR cycling conditions were 94°C for 10 sec, 45°C for 15 sec, and 72°C for 45 sec, for 30 cycles. All PCRs were performed in an Idaho Technology air thermal cycler using buffer containing 2 mM Mg²⁺.

PCR amplification products were separated by use of PCR Purity Plus gels and protocols (AT Biochem, Malvern, PA).

DNA Clones and Hybridization Probes. Clone pE31a was isolated from a genomic library prepared from the region of chromosome 7 linked to chloroquine resistance Walker-Jonah, *et al.* (1992), *Mol. Biochem. Parasitol.* 51, 313-320. Clone pS31H (GenBank accession no. L38454), containing an insert encompassing that of pE31a, was cloned from a size-selected Hind III restriction digest of Dd2 genomic DNA.

Clone pEBLe1 was cloned from a RT-PCR of Dd2 cDNA after amplification with primers UNIEBP5' (SEQ ID NO:23) and UNIEBP3' (SEQ ID NO:24). Clone pEBP1.2 (GenBank accession no. L38450), containing an insert encompassing that of pEBLe1, was isolated from a Dd2 cDNA library probed with pEBLe1. *DBL*-encoding sequences of *dbl-nm1-4* (GenBank accession no. L38455) and *dbl-nm1-5* (GenBank accession no. L38453) were amplified by RT-PCR from first strand cDNA of line Dd2/NM using primers UNIEBP5' and UNIEBP3'. Sequencing was performed on double stranded DNA templates by standard protocols for the dideoxynucleotide method. (Sequenase; U.S. Biochemicals).

Sequences related to the E31a sequence were detected with the 3005 bp insert of clone pS31H. The *eba-175* gene was detected with a PCR amplified probe consisting of the first 1825 bp of the coding sequence. *ebf-1* sequences were detected with the 2098 bp insert of clone pEBP1.2. All probes were comparable in organization, each containing a region encoding at least one *DBL* domain and varying amounts of flanking sequence.

Homology searches and alignments. Homology searches were performed with BLAST and the Genetics Computer Group program FASTA (Altschul, *et al.* (1990), *J. Mol. Biol.* 215, 403-410; Devereux, *et al.* (1984), *Nucleic Acids. Res.* 12(1 Pt 1, 387-395). Optimized alignments were produced with MACAW sequence alignment software (Schuler, *et al.* (1991), *Proteins.* 9, 180-190).

Multiple *P. falciparum* sequences encode DBL domains. Positional cloning experiments directed to *P. falciparum* chromosome 7 identified an ORF (E31a) encoding a *DBL* domain that is homologous to the domains found in the *P. vivax* and *P. knowlesi* DABPs and the *P. falciparum* SABP. Figure 4 shows the relative position of the E31a ORF on chromosome 7.

The homology between the *DBL* domains of E31a and the erythrocyte-binding proteins is due to the presence of short motifs of highly conserved amino acids. These well-conserved stretches are separated by non-homologous sequences and by deletions and insertions that vary the size of the domain by greater than 60 aa. The typical *DBL* domain contains 12 or more cysteine residues and has 7 conserved tryptophan residues. Additional

well conserved amino acids include 4 arginines, 3 aspartates, 9 positions with aliphatic residues (alanine, isoleucine, leucine, or valine) and 4 with aromatic amino acids (tryptophan, phenylalanine, or tyrosine).

Probes spanning the sequence that encodes the E31a *DBL* domain hybridized to multiple fragments within a single restriction digest and yielded bands that varied among parasite lines. The numerous distinct bands from a selection of different parasite DNAs indicated a large number of diverse but related elements. These multiple bands varied among different *P. falciparum* clones, in contrast to the well-conserved, single-copy signal obtained with the *eba-175* probe.

Because of the numerous cross-hybridizing sequences, it seemed likely that many of these related sequences would be on different chromosomes of the parasite. PFG electrophoresis of *P. falciparum* Dd2 chromosomes and hybridization with the E31a probe identified a number of cross-hybridizing sequences on multiple chromosomes. A control hybridization with the *eba-175* probe under identical conditions yielded a single band of hybridization from chromosome 7.

RNA Analysis of *DBL* Elements. Sequences from E31a (pS31H insert) were used to probe RNA blots for corresponding transcripts. No hybridization was detected. Because it was still possible that a message of low abundance was not being detected on the RNA blot, RT-PCR was used as a means of more sensitive detection. For this purpose, cDNA was generated by RT from random primers annealed to DNase-treated total RNA. E31a-specific oligonucleotides were then used to test for amplification from the cDNA. No amplification of the E31a sequence was obtained, while genomic DNA controls and amplification from cDNA by dihydrofolate reductase/thymidylate synthetase-specific primers yielded the expected bands. A screen of a cDNA library with E31a specific probes also failed to detect any clones hybridizing with the ORF. These results indicate that E31a is either a pseudogene, or is expressed in parasite strains or stages not examined in this work.

A PCR Method to Isolate Sequences Encoding *DBL* Domains. The identification of short conserved motifs in *DBL* domains that otherwise have extreme diversity led to a PCR strategy using degenerate oligonucleotide primers designed from conserved amino acid sequences in the *DBL* domains. Sequences PRRQKLC and PQFLRW were judged most suitable for minimizing degeneracy while allowing amplification of expressed *DBL* sequences. After these considerations and adjustment for *P. falciparum* codon usage, primers UNIEBP5' and UNIEBP3' were synthesized.

While some *P. falciparum* lines yielded similar patterns of amplified bands (*e. g.* Dd2 and MCamp; FCR3/A2 and K-1), no two separate isolates showed identical patterns, reflecting the diversity of the *DBL* domains in the parasite lines. A few bands of the same apparent size were present in many isolates. These included a consistent 490 bp product that was determined to be the *eba-175* gene by its expected size and hybridization to a gene-specific probe. The number of discernible bands probably underestimates the number of amplifiable sequences because of overlapping products of the same size and possible preferential amplification of some sequences over others. Nevertheless, the parasite-specific patterns in the amplified bands may provide a means to quickly type isolates and serves as a measure of parasite diversity in field samples.

To identify *DBL*-encoding sequences in RNA transcripts, the UNIEBP primers were used to amplify first-strand cDNAs generated from DNase-treated RNA preparations. Amplified products from Dd2, 3D7, HB3 and MCAMP cDNAs had diverse sizes ranging from 400 bp to nearly 1 kb. These included a band at 480-500 bp that was determined to be *eba-175* from its expected size and cross-hybridization to an *eba-175*-specific probe. Other bands were from amplification of different transcripts encoding *DBL* domains. Dd2-NM1 RNA, for example, yielded bands above the *eba-175* product that included two related sequences (*dbl-nm1-4*, *dbl-nm1-5*). These bands were found to be isolate-specific and to have features consistent with the *var* genes described in Example 3, below. Probes that detect *dbl-nm1-4* and *dbl-nm1-5* hybridized to multiple chromosomes and aligned more closely with E31a than with EBA-175 or DABP.

The RT-PCR amplifications also yielded a consistent band that encoded a novel *DBL* domain distinct from *eba-175*. A cDNA clone corresponding to this product was isolated by screening a λ gt10 Dd2 cDNA library with a radiolabeled *ebi-1* probe. Sequence from this and additional overlapping cDNA clones confirmed the conserved motifs of the *DBL* domain. The alignment of the predicted amino acid sequences showed that the *DBL* domain of *ebi-1* is more similar to *eba-175* than to the multicopy genes. There was, however, extensive divergence from *eba-175* and other known genes outside of the amplified region.

In contrast to the multicopy hybridization patterns of *dbl-nm1-4* and *dbl-nm1-5*, the *ebi-1* sequence, like that of *eba-175*, was found to have hybridization patterns consistent with a conserved single-copy gene. Probes specific for *ebi-1* hybridized only to chromosome 13, and restriction analysis with the enzymes *Cla* I, *Eco*RI, *Hind*III, *Hinf* I, *Nsi* I, *Rsa* I, and *Spe* I, all yielded bands expected from a single copy sequence. RNA blots probed with *ebi-1*-specific sequences showed several bands of hybridization, however, corresponding to 8-9.5 kb transcripts in mRNA from the Dd2 and 3D7 parasites. The transcripts of different size may result from alternative start and termination points or from incompletely processed species containing introns.

EXAMPLE 3: Isolation of *var* genes

Parasite clones, DNA analysis and Chromosome Mapping. Parasite clones were cultivated by the methods of (Trager, *et al.* (1976), *Science* 193, 673-675). DNA was extracted from parasite cultures as described (Peterson, *et al.* (1988), *Proc. Natl. Acad. Sci. USA* 85, 9114-9118) except that the DNA was as recovered by ethanol precipitation rather than spooling. Fingerprint analysis with the pC4.H32 probe was used to confirm DNA preparations (Dolan, *et al.* (1993), *Mol. Biochem. Parasitol.* 61, 137-142). Southern blotting to Nytran membranes was recommended by the manufacturer (Schleicher & Schuell, Keene, NH). PFG separation of the 14 *P. falciparum* chromosomes and chromosome mapping were performed as described (Wellems, *et al.* (1987), *Cell* 49, 633-642; Sinnis, *et al.* (1988); *Genomics* 3, 287-295).

RNA isolation. Parasites from 200 ml mixed stage cultures (5-10% parasitemia) were released by saponin lysis as for DNA preparations except that the procedures were performed with ice-cold solutions. RNA was immediately isolated from the parasite pellet by guanidine thiocyanate/phenol-chloroform methods, recovered and treated with RNAase-free DNase (Creedon, *et al.* (1994), *J. Biol. Chem.* 269, 16364-16370. RNA in H₂O was combined with 2 vol 100% ETOH, distributed into 2 ml vials and frozen as stock at -70°C. RNA was recovered by

precipitation with 0.1 vol 3M NaOAc. RNA blots were generated and probed as described (Creedon, *et al.* (1994), *J. Biol. Chem.* 269, 16364-16370).

YAC isolation, chromosome-segment libraries and cDNA libraries. Overlapping YACs spanning the 300 kb segment of chromosome 7 that contains the CQR locus were obtained from a YAC library of a CQR FCR3 parasite line de Bruin, *et al.* (1992), *Genomics* 14, 332-339) by the procedures of Lanzer, *et al.* (1993), *Nature* 361, 654-657. Orientation of the YACs and their overlaps were identified with probes obtained from the YAC ends by inverted PCR.

Attempts to construct cosmid libraries and large insert (~ 10 kb) λ libraries from high molecular weight *P. falciparum* genomic DNA yielded only rearranged clones. An alternative approach was therefore taken in which chromosome-segment libraries were constructed that contained small (0.5-5 kb) inserts in plasmid vectors. Plasmid libraries containing *AluI*, *HinfI*, *RsaI* and *SspI* inserts in pCDNAII were constructed from Dd2 chromosome 7 restriction fragments purified by pulsed-field gel (PFG) electrophoresis (Wellems, *et al.* (1991), *Proc. Natl. Acad. Sci. USA* 88, 3382-3386). A plasmid library from a 34 kb *Apal-SmaI* restriction fragment of YAC PfYED9 was constructed by the same methods. Inserts in the plasmid libraries were generally 0.5-4 kb.

The λ gt10 Dd2 cDNA library was prepared under contract by CloneTech Laboratories Inc. (Palo Alto, CA) from the DNase-treated, polyA+ fraction of Dd2 RNA. The cDNA was generated in two separate reactions using oligodT primers or random primers. Products of these reactions were combined, processed and cloned into the EcoRI site of λ gt10. 1.6×10^6 independent recombinants were obtained and amplified.

Isolation of overlapping clones and DNA sequencing. Plasmid clones from the chromosome-segment and YAC-segment libraries were picked at random and their locations were established by restriction mapping. After sequence data from these clones were generated, overlapping clones were isolated in a process of "chromosome walking" by rescreening the libraries with oligonucleotide probes near the ends of sequenced inserts. Sufficient divergence was present among repetitive elements in the sequences to allow distinction of clones and unambiguous assignment of overlaps (generally 50-200 bp).

Sequencing reactions with single-strand M13 DNA (1 μ g) and double-strand plasmid DNA (2-5 μ g) were performed in 96-well polyvinyl chloride U-bottom microassay plates using a Sequenase protocol recommended by United States Biochemical Corp. (Cleveland, OH). Reactions were separated by 8M urea-6% polyacrylamide sequencing gels and exposed to Kodak BioMax MR film. Sequence data from some clones were also obtained by use of an ABI 373A automated DNA sequencer (Applied Biosystems Inc., Foster City, CA). Cycle sequencing reactions were performed using the ABI PRISM DyeDeoxy system.

DNA sequence editing, analyses and display were performed with MacVector software (International Biotechnologies Inc., New Haven, CT), BLAST (Altschul, *et al.* (1990), *J. Mol. Biol.* 215, 403-410), Genetics Computer Group programs (Devereux, *et al.* (1984), *Nucleic Acids Res.* 12, 387-395) and the DNADRAW package (Shapiro, *et al.* (1986), *Nucleic Acids Res.* 14, 65-73) maintained at the National Institutes of Health.

Identification of a large hypervariable region within a chromosome 7 segment linked to chloroquine resistance. Four overlapping yeast artificial chromosomes from the *P. falciparum* FCR3 line were obtained that span the 300 kb chromosome segment linked to CQR, a segment located 300-600 kb from the telomere of chromosome

7. Figure 5 shows the positions of these YACs (PfYEF2, PfYFE6, PfYKF8, PfYED9) relative to the chromosome map. In order to define the structure of this 300 kb segment, we performed comparative hybridizations to search for polymorphisms between parasite lines. Clones were randomly picked from chromosome segment-specific plasmid libraries and their inserts were hybridized against restriction digests of the YAC and parasite DNAs. Over thirty
5 inserts were identified that recognized PfYEF2, PfYFE6 or PfYKF8 and showed a predomance of single copy sequences with few polymorphisms (*AluI*, *HinI*, *RsaI* and *SspI* digests), consistent with prior findings that chromosome internal regions are largely conserved and contain a preponderance of single copy sequences. However, fifteen other inserts that recognized PfYED9 showed highly polymorphic sets of repetitive elements in the parasite DNAs. Southern analysis indicated that these polymorphic elements were part of a chromosome hypervariable region
10 contained within the PfYED9 clone.

Mapping and DNA sequencing of the hypervariable region spanned by YAC PfYED9. Single copy sequences detected by pE45b and pH270.5 flank the hypervariable region spanned by PfYED9 (Figure 5). The pE45b and pH270.5 probes were therefore used to assign large restriction fragments on the PfYED9 map and establish enzyme recognition sites as reference points. A detailed restriction map of the PfYED9 hypervariable region was then
15 developed. Fifteen overlapping clones ("a"- "f" and "h"- "o" in Figure 5) were isolated by a chromosome walking approach from Dd2 chromosome subsegment libraries (Wellems *et al.*, *supra*) The inserts yielded 19.1 kb of continuous Dd2 sequence having predicted enzyme recognition sites in perfect accord with the PfYED9 restriction map. Such agreement indicates that the Dd2 and FCR3 sequences in this part of the chromosome are very similar, despite differences elsewhere in the genome that are evident by restriction analysis.

20 We also obtained genomic sequence data from the 34 kb *Apal-SmaI* fragment of PfYED9. Purified PfYED9 DNA was cut with *SmaI* to yield a 110 kb fragment, which was then isolated by PFG electrophoresis and digested with *Apal*. The resulting 34 kb *Apal-SmaI* band was purified by PFG electrophoresis, digested in four separate reactions by *AluI*, *HinI*, *RsaI* or *SspI* and incorporated into a plasmid (PCDNAII) library. Cloned inserts from the library were checked for hybridization to the PfYED9 34 kb fragment, assigned to the PfYED9 map and
25 sequenced (Figure 5). Overlapping inserts were obtained by the chromosome walking approach except for three gaps ("t", "z", "θ" in Figure 5) which were closed by PCR amplification of PfYED9 DNA using primers from flanking sequences. The clones from PfYED9 ("r"- "z", "γ", "κ" and "α" + "β" in Figure 5) yielded 22.2 kb of continuous DNA sequence that overlaps the Dd2 sequence at the "f"/"β" junction and has predicted restriction sites that match the PfYED9 map perfectly. The composite sequence from the Dd2 and PfYED9 segments is 40,171 kb.

30 Structure of a *var* gene cluster and comparative analysis of predicted amino acid sequences. The 40,171 bp sequence contains three 10-12 kb regions that have related sequences and structure. Each of these regions harbors a pair of ORFs. The first ORF in each pair begins with a consensus ATG start codon preceded by typical *P. falciparum* non-coding sequence of abundant A+T content. The ORFs of each pair are separated by an intervening AT-rich and non-coding sequence of 0.9 kb to 1.1 kb. Presence of consensus intron-exon splice junction sequences
35 at either end of these intervening sequences and lack of a consistent translation start site in the 3' ORF indicate that the each pair of ORFs belongs to an individual gene having a two exon structure. This has been verified by

comparison of the genomic sequences to the cDNA sequence of an expressed gene (*var-7*; see subsequent section). The three 10 kb to 12 kb regions thus contain members of a variant gene family which have coding regions of 9.23kb (*var-1*), 7.99 kb (*var-2*) and 9.01 kb (*var-3*). Predicted molecular weights of the encoded proteins are 350 kD, 302 kD and 344 kD, respectively.

5 The *var* genes are flanked by additional members of the *var* family in PfYED9. Restriction analysis identified two additional genes that are 12-35 kb upstream of the sequenced region and are closely related to *var-2* and *var-3* (*var-2c* and *Var-3c*, Figure 5). The *var* genes thus have a clustered arrangement in which many individual members are organized in head-to-tail fashion. Between *var-1* and *var-2* is a 5 kb DNA sequence that harbors a short ORF homologous to that of a repetitive element (rij) suggested to be a transposable element in *P. falciparum*.

10 The deduced protein sequences of the *var* genes are highly diverse, yet all contain certain conserved motifs and common structural features. Database searches identified 2 to 4 domains within each *var* sequence that are homologous to cysteine-rich domains of SABP and DABP. In the *var* sequences, the first domain near the amino-terminus (DBL domain 1) is the most conserved of the DBL domains and has amino acid signatures that differentiate it from subsequent domains (e.g. consensus peptide sequences GAcAp[Y/F]rrL, CTxLARsfadlgdIVgrdLYLG and VPTYFDYVpqlrwF). Between DBL domains 1 and 2 is another type of conserved domain, a cysteine-rich interdomain region (CIDR) of 300-400 amino acids. The CIDR does not have all the motifs of a DBL domain, but it does have a region at the 3' end which is homologous to the end of the FI DBL domain in SABP. The conservation evident in the sequences of DBL domain I and the CIDR suggest that these regions maintain important structures in the head of the variant molecule.

20 DBL domains 2, 3 and 4 (numbering is according to *var-1*, the first sequence completed) have less discriminating signatures than domain 1, and show features of cross-alignment and variation in number that suggest these domains can undergo shuffling and deletion.

25 DBL domain 4 is followed by a segment of variable length and a hydrophobic region that is encoded at the end of the first exon (exon 1). In all *var* sequences this hydrophobic region fits the criteria of a transmembrane segment. The second exon (exon II) encodes a large (45-55 kD) conserved C-terminal sequence that has an acid character (predicted pI = 4.5, vs. 5.9 for the part of the protein upstream of the splice junction) and a cysteine content of < 1% (vs. > 4% upstream). The position of this C-terminal sequence downstream of a single transmembrane segment suggests that it has a cytoplasmic location.

30 No consensus signal sequence was detected in the NH₂-terminal region of the predicted *var* ORFs. We note the presence of several motifs in the protein sequences that are known to act as ligands and receptors in the integrin family. These include RGD (*var-1* codons 886-88, 1992-94) and DGEA (*var-1* codons 2111-14). Not all of these motifs occur in each protein sequence and, when they do occur, their positions vary.

35 Identification of *var* transcripts and chromosome expression sites. To identify transcribed *var* sequences we screened a λ gt10 Dd2 cDNA library with *var*-containing *Bss*III restriction fragments that had been purified from PfYED9 and radiolabeled by random hexamer priming. This screening yielded 18 clones with inserts that hybridized back to PfYED9. By cross-hybridization studies and DNA sequence analysis the inserts fell into two groups: group

I inserts that aligned with sequences of *var* exon I (AT240, AT242, AT244, AT284, AT287, AT288, AT295, AT296); and group II inserts that aligned with sequences of *var* exon II (AT140, AT141, AT142, AT145, AT147, AT148, AT150, AT152).

5 The full ORF of an expressed *var* gene (*var-7*) was determined from AT242 and overlapping cDNA clones that were obtained by a PCR-based walking strategy. The sequence showed that *var-7* has a 6.6 kb ORF containing two *DBL* domains, a hydrophobic transmembrane sequence and carboxy-terminal region typical of *var* genes (predicted molecular weight 249 kD). Comparison of *var-7* with the *var-1* sequence demonstrated continuity of the alignments at the predicted splice junction between the ORFs of exons I and II. PCR amplification of Dd2 genomic DNA was also performed with primers derived from the two *var-7* exons. Sequence of this *var-7* PCR product 10 confirmed consensus splice sites and a 1 kb intron typical of the *var* genes. Transcription of *var-7* was detected as a 7.5 kb band by RNA blot analysis.

Chromosome mapping experiments with a *var-7*-specific probe localized the *var-7* gene to a region that is 600 kb from one end of Dd2 chromosome 12 (chromosome 12 has a length of 2600 kb). No hybridization of the *var-7* probe was detected to any other Dd2 chromosome nor to any chromosomes of the HB3, 3D7 or A4 15 parasites. Other cDNA inserts from the group I clones were also sequenced and examined for chromosome hybridization signals. The AT240 cDNA insert mapped to the *var-1/var-2/var-3* cluster on Dd2 chromosome 7 and its sequence matched that of *var-3*. The AT244, AT284, AT287, AT288, AT295 and AT296 inserts all showed overlapping sequences and yielded the same hybridization patterns. Chromosome sites recognized by these inserts included regions within two *Sma*I fragments from Dd2 chromosome 7 and another from chromosome 9. We note 20 that loss of a cytoadherence phenotype has been correlated with a chromosome 9 deletion in certain *P. falciparum* lines.

1.8 kb to 2.4 kb RNA transcripts related to *var* exon II. In addition to the 7.5 kb *var-7* band, a broad 1.8 kb to 2.4 kb band was detected on RNA blots after hybridization with a probe that recognizes *var* exon II. Sequences of eight group II cDNA inserts homologous to exon II were therefore determined and aligned against the 25 *var* genes. Comparative analysis of the insert sequences showed that all differed from one another in regions of overlap, indicating that transcription of the corresponding RNAs was from different loci. Three of the cDNA sequences (AT140, AT141 and AT148) aligned downstream of the intron/exon II splice junction. However, five other cDNA inserts (AT142, AT145, AT147, AT150 and AT152) had sequences that aligned upstream of the *var* intron/exon II splice site and included regions homologous to *var* intron sequences. In the vicinity of the splice 30 junction, consensus splice sites occurred in three of the cDNA sequences (AT142, AT147, AT150) while a fourth sequence (AT145) showed the required AG dinucleotide but not the expected pyrimidine tract of the splice consensus. The part of the fifth sequence (AT152) that aligned with the *var* intron extended upstream only to the TAG of the splice sequence. All five sequences lacked a consensus start codon preceded by A+T-rich non-coding DNA that is typical of *P. falciparum* translation start sites.

35 Isolate-specific *var* sequences and evidence for DNA recombination in cultivated parasite clones. The diversity of *var* forms expressed by *P. falciparum* parasites reflects a tremendous repertoire in the *var* gene family.

This repertoire is evident in the patterns of restriction polymorphism detected by *var* probes as well as in the detection of *var*-specific sequences that hybridize to some parasite DNAs but not to others. The *var-7* gene expressed by Dd2, for example, is not present in the HB3, 3D7 or A4 genomes. Such *var* diversity suggests that frequent DNA rearrangements underlie the production of antigenically variant types in different parasite strains.

5 To test for DNA rearrangements in parasites cultivated *in vitro*, we used *var* sequences to probe restricted DNAs from Dd2 lines adapted to neuraminidase-treated erythrocytes. In one rearrangement a novel 35 kb *Bgl*I fragment is seen in NM1 DNA probed with the λ T142 (group II) insert. In another rearrangement a deletion of a 20 kb *Pst*I band is evident in NM8 DNA probed with a *var-7* sequence. Deletion of this 20 kb band was also detected in the Dd2/R8 subclone obtained before neuraminidase selection, indicating that the DNA rearrangement was
10 not produced by selection in neuraminidase-treated erythrocytes.

The above examples are provided to illustrate the invention and other variants of the invention encompassed by the claims will be readily apparent to one of ordinary skill in the art.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

- 5 (i) APPLICANT: The United States, As Represented by the
Secretary, Department of Health and Human Services
- (ii) TITLE OF INVENTION: BINDING DOMAINS FROM PLASMODIUM VIVAX
AND PLASMODIUM FALCIPARUM ERYTHROCYTE BINDING PROTEINS
- 10 (iii) NUMBER OF SEQUENCES: 45
- (iv) CORRESPONDENCE ADDRESS:
- 15 (A) ADDRESSEE: Knobbe Martens Olson & Bear
(B) STREET: 620 Newport Center Drive 16th Floor
(C) CITY: Newport Beach
(D) STATE: California
(E) COUNTRY: US
(F) ZIP: 92660
- 20 (v) COMPUTER READABLE FORM:
- (A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
25 (D) SOFTWARE: PatentIn Release #1.0, Version #1.25
- (vi) CURRENT APPLICATION DATA:
- (A) APPLICATION NUMBER:
(B) FILING DATE:
30 (C) CLASSIFICATION:
- (vii) PRIOR APPLICATION DATA
- (A) APPLICATION NUMBER: US08/487826
(B) FILING DATE: 07-JUN-1996
- 35 (viii) ATTORNEY/AGENT INFORMATION:
- (A) NAME: Israelsen, Ned
(B) REGISTRATION NUMBER: 29,655
(C) REFERENCE/DOCKET NUMBER: NIH121.001QPC
- 40 (ix) TELECOMMUNICATION INFORMATION:
- (A) TELEPHONE: (619) 235-8550
(B) TELEFAX: (619) 235-0176

45 (2) INFORMATION FOR SEQ ID NO:1:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 4084 base pairs
(B) TYPE: nucleic acid
50 (C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: DNA (genomic)
- 55 (iii) HYPOTHETICAL: NO
- (vi) ORIGINAL SOURCE:
- (A) ORGANISM: Plasmodium vivax
- 60 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

AAGCTTTTAA AAATAGCAAC AAAATTTCTGA AACATTGCCA CAAAATTTT ATGTTTTACA 60
TATATTTAGA TTCATACAAT TTAGGTGTAC CCTGTTTTTT GATATATGCG CTAAATTTT 120

TTTTTCGCTC ATATGTTTATG TTATATGTGT AGAACAACTT GCTGAATAAA TTACGTACAC 180
TTTCTGTTCT GAATAATATT ACCACATACA TTTAATTTTA AATACTATGA AAGGAAAAAA 240
CCGCTCTTTA TTTGTTCTCC TAGTTTTATT ATTGTTACAC AAGGTATCAT ATAAGGATGA 300
TTTTTCTATC AACTAATAA ATTATCATGA AGGAAAAAA TATTTAATTA TACTAAAAAG 360
5 AAAATTAGAA AAAGCTAATA ATCGTGTGT TTGCAATTTT TTTCTTCATT TCTCTCAGGT 420
AAATAATGTA TTATTAGAAC GAACAATTGA AACCCTTCTA GAATGCAAAA ATGAATATGT 480
GAAAGGTGAA AATGGTTATA AATTAGCTAA AGGACACCAC TGTGTTGAGG AAGATAACTT 540
AGAACGATGG TTACAAGGAA CCAATGAAAG AAGAAGTGAG GAAAATATAA AATATAAATA 600
TGGAGTAACG GAACTAAAAA TAAAGTATGC GCAATGAAT GGAAAAAGAA GCAGCCGCAT 660
10 TTTGAAGGAA TCAATTTACG GGGCGCATAA CTTTGGAGGC AACAGTTACA TGGAGGGAAA 720
AGATGGAGGA GATAAACTG GGGAGGAAAA AGATGGAGAA CATAAACTG ATAGTAAAC 780
TGATAACGGG AAAGGTGCAA ACAATTTGGT AATGTTAGAT TATGAGACAT CTAGCAATGG 840
CCAGCCAGCG GGAACCCTTG ATAATGTTCT TGAATTTGTG ACTGGGCATG AGGGAAATTC 900
TCGTAAAAAT TCCTCGAATG GTGGCAATCC TTACGATATT GATCATAAGA AAACGATCTC 960
15 TAGTGCTATT ATAAATCATG CTTTTCTTCA AAATACTGTA ATGAAAACT GTAATTATAA 1020
GAGAAACGT CGGGAAGAG ATTGGGACTG TAACACTAAG AAGGATGTTT GTATACCAGA 1080
TCGAAGATAT CAATTATGTA TGAAGGAAT TACGAATTTG GTAAATAATA CAGACACAAA 1140
TTTTTCATAGG GATATAACAT TTCGAAAATT ATATTTGAAA AGGAACTTA TTTATGATGC 1200
TGCAGTAGAG GGCGATTTAT TACTTAAGTT GAATAACTAC AGATATAACA AAGACTTTTG 1260
20 CAAGGATATA AGATGGAGTT TGGGAGATTT TGGAGATATA ATTATGGGAA CCGATATGGA 1320
AGGCATCGGA TATTCCAAAG TAGTGGAATA TAATTTGCGC AGCATCTTTG GAACTGATGA 1380
AAAGGCCCAA CAGCGTCGTA AACAGTGGTG GAATGAATCT AAAGCACAAA TTTGGACAGC 1440
AATGATGTAC TCAGTTAAAA AAAGATTAAA GGGGAATTTT ATATGGATTT GTAAATTAAA 1500
TGTTGCGGTA AATATAGAAC CGCAGATATA TAGATGGATT CGAGAATGGG GAAGGGATTA 1560
25 CGTGTCAAGG TTGCCCACAG AAGTGCAAAA ACTGAAAGAA AAATGTGATG GAAAAATCAA 1620
TTATACTGAT AAAAAAGTAT GTAAGGTACC ACCATGTCAA AATGCGTGA AATCATATGA 1680
TCAATGGATA ACCAGAAAAA AAAATCAATG GGATGTTCTG TCAAATAAAT TCATAAGTGT 1740
AAAAAACGCA GAAAAGGTTT AGACGGCAGG TATCGTAACT CCTTATGATA TACTAAAACA 1800
GGAGTTAGAT GAATTTAAGC AGGTGGCTTT TGAGAATGAA ATTAACAAAC GTGATGGTGC 1860
30 ATATATTGAG TTATGCGTTT GTTCCGTTGA AGAGGCTAAA AAAAATACTC AGGAAGTTGT 1920
GACAAATGTG GACAATGCTG CTAAATCTCA GCCCACCAT TCAAATCCGA TAAGTCAGCC 1980
TGATAGTAGT AGTAAAGCGG AGAAGGTTCC AGGAGATTCT ACGCATGGAA ATGTTAACAG 2040
TGGCCAAGAT AGTTCTACCA CAGGTAAAGC TGTTACGGGG GATGGTCAAA ATGGAAATCA 2100
GACACCTGCA GAAAGCGATG TACAGCGAAG TGATATTGCC GAAAGTGTA GTGCTAAAAA 2160
35 TGTTGATCCG CAGAAATCTG TAAGTAAAAG AAGTGACGAC ACTGCAAGCG TTACAGGTAT 2220
TGCCGAAGAT GGAAGGAAA ACTTAGGCGC ATCAAATAGT CGACCTTCTG AGTCCACCGT 2280
TGAAGCAAT AGCCAGGTG ATGATACTGT GAACAGTGCA TCTATACCTG TAGTGAGTGG 2340
TGAAAACCCA TTGGTAACCC CCTATAATGG TTTGAGGCAT TCGAAAGACA ATAGTGATAG 2400
CGATGGACCT GCGGAATCAA TGGCGAATCC TGATTCAAAT AGTAAAGGTG AGACGGGAAA 2460
40 GGGGCAAGAT AATGATATGG CGAAGGCTAC TAAAGATAGT AGTAATAGTT CAGATGGTAC 2520
CAGCTCTGCT ACGGGTGATA CTACTGATGC AGTTGATAGG GAAATTAATA AAGGTGTTCC 2580
TGAGGATAGG GATAAACTG TAGGAAGTAA AGATGGAGGG GGGGAAGATA ACTCTGCAAA 2640
TAAGGATGCA GCGACTGTAG TTGGTGAGGA TAGAATTCGT GAGAACAGCG CTGGTGGTAG 2700
CACTAATGAT AGATCAAAAA ATGACACGGA AAAGAACGGG GCCTCTACCC CTGACAGTAA 2760
45 ACAAAGTGAG GATGCAACTG CGCTAAGTAA AACCAGAAAGT TTAGAATCAA CAGAAAGTGG 2820
AGATAGAACT ACTAATGATA CAACTAACAG TTTAGAAAAT AAAAATGGAG GAAAAGAAAA 2880
GGATTTACAA AAGCATGATT TTAAGGTAA TGATACGCCG AATGAAGAAC CAAATTCTGA 2940
TCAAACATCA GATGCAGAAG GACATGACAG GGATAGCATC AAAAATGATA AAGCAGAAAG 3000
GAGAAAGCAT ATGAATAAAG ATACTTTTAC GAAAAATACA AATAGTCACC ATTTAAATAG 3060
50 TAATAATAAT TTGAGTAATG GAAAATTAGA TATAAAGAA TACAAATACA GAGATGTCAA 3120
AGCAACAAGG GAAGATATTA TATTAATGTC TTCAGTACGC AAGTGCAACA ATAATATTTT 3180
TTTAGAGTAC TGTAACCTCTG TAGAGGACAA AATATCATCG AATACTTGT TTAGAGAGAA 3240
AAGTAAAAAT TTATGTTGCT CAATATCGGA TTTTGTGTTG AACTATTTTG ACGTGTATTC 3300
TTATGAGTAT CTTAGCTGCA TGAAAAAGGA ATTTGAAGAT CCATCTTACA AGTGCTTTAC 3360
55 GAAAGGGGGC TTTAAAGGTA TGCAGAAAAA GATGCTGAAT AGAGAAAGGT GTTGAGTAAA 3420
TTAAAAAGGA ATTAATTTTA GGAATGTTAT AAACATTTTT GTACCCAAAA TTCTTTTTGC 3480
AGACAAGACT TACTTTGCGG CGGCGGGAGC GTTGCTGATA CTGCTGTTGT TAATTGCTTC 3540
AAGGAAGATG ATCAAAAATG AGTAACCAGA AAATAAATA AAATAACATA AAATAAATA 3600
AAAACATGAA TAACAATTAA AATAAATAA AATGAGAAAT GCCTGTTAAT GCACAGTTAA 3660
60 TTCTAACGAT TCCATTTGTG AAGTTTTTAA GAGAGCAAA ATGCATAGTC ATTATGTCCA 3720
TGCATATATA CACATATATG TACGTATATA TAATAACGC AACTTTCTT GTTCGTACAG 3780
TTCTGAAGAA GCTACATTTA ATGAGTTTGA AGAATACTGT GATAATATTC ACAGAAATCCC 3840
TCTGATGCCT AACAGTAATT CAAATTTCAA GAGCAAAAT CCATTTAAAA AGAAATGTTA 3900
CATCATTTTG CGTTTTTCTT TTTTTCTTTT TTTTCTTTT TTTAGATATT GAACACATGC 3960

AGCCATCAAC CCCCCTGGAT TATTCATGAT GCTACTTTGG TAAGTAAAAG CAATTCTGAT 4020
 TGTAGTGCTG ATGTAATTTT AGTCATTTTG CTTGCTGCAA TAAACGAGAA AATATATCAA 4080
 GCTT 4084

5 (2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1115 amino acids

(B) TYPE: amino acid

10 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

15 (iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Plasmodium vivax

20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

1	Met	Lys	Gly	Lys	Asn	Arg	Ser	Leu	Phe	Val	Leu	Leu	Val	Leu	Leu	Leu
				5					10					15		
25	Leu	His	Lys	Val	Ser	Tyr	Lys	Asp	Asp	Phe	Ser	Ile	Thr	Leu	Ile	Asn
			20					25					30			
	Tyr	His	Glu	Gly	Lys	Lys	Tyr	Leu	Ile	Ile	Leu	Lys	Arg	Lys	Leu	Glu
			35					40				45				
	Lys	Ala	Asn	Asn	Arg	Asp	Val	Cys	Asn	Phe	Phe	Leu	His	Phe	Ser	Gln
		50					55				60					
30	Val	Asn	Asn	Val	Leu	Leu	Glu	Arg	Thr	Ile	Glu	Thr	Leu	Leu	Glu	Cys
		65			70					75					80	
	Lys	Asn	Glu	Tyr	Val	Lys	Gly	Glu	Asn	Gly	Tyr	Lys	Leu	Ala	Lys	Gly
			85						90					95		
	His	His	Cys	Val	Glu	Glu	Asp	Asn	Leu	Glu	Arg	Trp	Leu	Gln	Gly	Thr
			100						105				110			
35	Asn	Glu	Arg	Ser	Glu	Glu	Asn	Ile	Lys	Tyr	Lys	Tyr	Gly	Val	Thr	
			115					120					125			
	Glu	Leu	Lys	Ile	Lys	Tyr	Ala	Gln	Met	Asn	Gly	Lys	Arg	Ser	Ser	Arg
		130					135				140					
40	Ile	Leu	Lys	Glu	Ser	Ile	Tyr	Gly	Ala	His	Asn	Phe	Gly	Gly	Asn	Ser
		145				150				155					160	
	Tyr	Met	Glu	Gly	Lys	Asp	Gly	Gly	Asp	Lys	Thr	Gly	Glu	Glu	Lys	Asp
			165						170					175		
	Gly	Glu	His	Lys	Thr	Asp	Ser	Lys	Thr	Asp	Asn	Gly	Lys	Gly	Ala	Asn
45			180						185					190		
	Asn	Leu	Val	Met	Leu	Asp	Tyr	Glu	Thr	Ser	Ser	Asn	Gly	Gln	Pro	Ala
			195					200					205			
	Gly	Thr	Leu	Asp	Asn	Val	Leu	Glu	Phe	Val	Thr	Gly	His	Glu	Gly	Asn
		210					215					220				
50	Ser	Arg	Lys	Asn	Ser	Ser	Asn	Gly	Gly	Asn	Pro	Tyr	Asp	Ile	Asp	His
			225			230				235					240	
	Lys	Lys	Thr	Ile	Ser	Ser	Ala	Ile	Ile	Asn	His	Ala	Phe	Leu	Gln	Asn
			245							250				255		
	Thr	Val	Met	Lys	Asn	Cys	Asn	Tyr	Lys	Arg	Lys	Arg	Arg	Glu	Arg	Asp
55			260						265					270		
	Trp	Asp	Cys	Asn	Thr	Lys	Lys	Asp	Val	Cys	Ile	Pro	Asp	Arg	Arg	Tyr
			275					280					285			
	Gln	Leu	Cys	Met	Lys	Glu	Leu	Thr	Asn	Leu	Val	Asn	Asn	Thr	Asp	Thr
		290					295					300				
60	Asn	Phe	His	Arg	Asp	Ile	Thr	Phe	Arg	Lys	Leu	Tyr	Leu	Lys	Arg	Lys
		305				310				315					320	
	Leu	Ile	Tyr	Asp	Ala	Val	Glu	Gly	Asp	Leu	Leu	Leu	Lys	Leu	Asn	
			325						330					335		
	Asn	Tyr	Arg	Tyr	Asn	Lys	Asp	Phe	Cys	Lys	Asp	Ile	Arg	Trp	Ser	Leu

340 345 350
 Gly Asp Phe Gly Asp Ile Ile Met Gly Thr Asp Met Glu Gly Ile Gly
 355 360 365
 Tyr Ser Lys Val Val Glu Asn Asn Leu Arg Ser Ile Phe Gly Thr Asp
 370 375 380
 Glu Lys Ala Gln Gln Arg Lys Lys Gln Trp Trp Asn Glu Ser Lys Ala
 385 390 395 400
 Gln Ile Trp Thr Ala Met Met Tyr Ser Val Lys Lys Arg Leu Lys Gly
 405 410 415
 Asn Phe Ile Trp Ile Cys Lys Leu Asn Val Ala Val Asn Ile Glu Pro
 420 425 430
 Gln Ile Tyr Arg Trp Ile Arg Glu Trp Gly Arg Asp Tyr Val Ser Glu
 435 440 445
 Leu Pro Thr Glu Val Gln Lys Leu Lys Glu Lys Cys Asp Gly Lys Ile
 450 455 460
 Asn Tyr Thr Asp Lys Lys Val Cys Lys Val Pro Pro Cys Gln Asn Ala
 465 470 475 480
 Cys Lys Ser Tyr Asp Gln Trp Ile Thr Arg Lys Lys Asn Gln Trp Asp
 485 490 495
 Val Leu Ser Asn Lys Phe Ile Ser Val Lys Asn Ala Glu Lys Val Gln
 500 505 510
 Thr Ala Gly Ile Val Thr Pro Tyr Asp Ile Leu Lys Gln Glu Leu Asp
 515 520 525
 Glu Phe Asn Glu Val Ala Phe Glu Asn Glu Ile Asn Lys Arg Asp Gly
 530 535 540
 Ala Tyr Ile Glu Leu Cys Val Cys Ser Val Glu Glu Ala Lys Lys Asn
 545 550 555 560
 Thr Gln Glu Val Val Thr Asn Val Asp Asn Ala Ala Lys Ser Gln Ala
 565 570 575
 Thr Asn Ser Asn Pro Ile Ser Gln Pro Val Asp Ser Ser Lys Ala Glu
 580 585 590
 Lys Val Pro Gly Asp Ser Thr His Gly Asn Val Asn Ser Gly Gln Asp
 595 600 605
 Ser Ser Thr Thr Gly Lys Ala Val Thr Gly Asp Gly Gln Asn Gly Asn
 610 615 620
 Gln Thr Pro Ala Glu Ser Asp Val Gln Arg Ser Asp Ile Ala Glu Ser
 625 630 635 640
 Val Ser Ala Lys Asn Val Asp Pro Gln Lys Ser Val Ser Lys Arg Ser
 645 650 655
 Asp Asp Thr Ala Ser Val Thr Gly Ile Ala Glu Ala Gly Lys Glu Asn
 660 665 670
 Leu Gly Ala Ser Asn Ser Arg Pro Ser Glu Ser Thr Val Glu Ala Asn
 675 680 685
 Ser Pro Gly Asp Asp Thr Val Asn Ser Ala Ser Ile Pro Val Val Ser
 690 695 700
 Gly Glu Asn Pro Leu Val Thr Pro Tyr Asn Gly Leu Arg His Ser Lys
 705 710 715 720
 Asp Asn Ser Asp Ser Asp Gly Pro Ala Glu Ser Met Ala Asn Pro Asp
 725 730 735
 Ser Asn Ser Lys Gly Glu Thr Gly Lys Gly Gln Asp Asn Asp Met Ala
 740 745 750
 Lys Ala Thr Lys Asp Ser Ser Asn Ser Ser Asp Gly Thr Ser Ser Ala
 755 760 765
 Thr Gly Asp Thr Thr Asp Ala Val Asp Arg Glu Ile Asn Lys Gly Val
 770 775 780
 Pro Glu Asp Arg Asp Lys Thr Val Gly Ser Lys Asp Gly Gly Gly Glu
 785 790 795 800
 Asp Asn Ser Ala Asn Lys Asp Ala Ala Thr Val Val Gly Glu Asp Arg
 805 810 815
 Ile Arg Glu Asn Ser Ala Gly Gly Ser Thr Asn Asp Arg Ser Lys Asn
 820 825 830
 Asp Thr Glu Lys Asn Gly Ala Ser Thr Pro Asp Ser Lys Gln Ser Glu
 835 840 845
 Asp Ala Thr Ala Leu Ser Lys Thr Glu Ser Leu Glu Ser Thr Glu Ser

850 855 860
 Gly Asp Arg Thr Thr Asn Ser Thr Thr Asn Ser Leu Glu Asn Lys Asn
 865 870 875 880
 Gly Gly Lys Glu Lys Asp Leu Gln Lys His Asp Phe Lys Ser Asn Asp
 885 890 895
 Thr Pro Asn Glu Glu Pro Asn Ser Asp Gln Thr Thr Asp Ala Glu Gly
 900 905 910
 His Asp Arg Asp Ser Ile Lys Asn Asp Lys Ala Glu Arg Lys His
 915 920 925
 Met Asn Lys Asp Thr Phe Thr Lys Asn Thr Asn Ser His His Leu Asn
 930 935 940
 Ser Asn Asn Asn Leu Ser Asn Gly Lys Leu Asp Ile Lys Glu Tyr Lys
 945 950 955 960
 Tyr Arg Asp Val Lys Ala Thr Arg Glu Asp Ile Ile Leu Met Ser Ser
 965 970 975
 Val Arg Lys Cys Asn Asn Asn Ile Ser Leu Glu Tyr Cys Asn Ser Val
 980 985 990
 Glu Asp Lys Ile Ser Ser Asn Thr Cys Ser Arg Glu Lys Ser Lys Asn
 995 1000 1005
 Leu Cys Cys Ser Ile Ser Asp Phe Cys Leu Asn Tyr Phe Asp Val Tyr
 1010 1015 1020
 Ser Tyr Glu Tyr Leu Ser Cys Met Lys Lys Glu Phe Glu Asp Pro Ser
 1025 1030 1035 1040
 Tyr Lys Cys Phe Thr Lys Gly Gly Phe Lys Ile Asp Lys Thr Tyr Phe
 1045 1050 1055
 Ala Ala Ala Gly Ala Leu Leu Ile Leu Leu Leu Ile Ala Ser Arg Lys
 1060 1065 1070
 Met Ile Lys Asn Asp Ser Glu Glu Ala Thr Phe Asn Glu Phe Glu Glu
 1075 1080 1085
 Tyr Cys Asp Asn Ile His Arg Ile Pro Leu Met Pro Asn Asn Ile Glu
 1090 1095 1100
 His Met Gln Pro Ser Thr Pro Leu Asp Tyr Ser
 1105 1110 1115

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 4507 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Plasmodium falciparum

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

TATATATATA TATATATATA GATAATAACA TATAAATATA TTCAATGTGC ATACAATGAA 60
 ATGTAATATT AGTATATATT TTTTGTCTTC CTCTTTGTG TTATATTTTG CAAAAGCTAG 120
 GAATGAATAT GATATAAAG AGAATGAAAA ATTTTGTAGAC GTGTATAAAG AAAAATTTAA 180
 TGAATTAGAT AAAAAGAAAT ATGGAAATGT TCAAAAACT GATAAGAAAA TATTACTTT 240
 TATAGAAAAT AAATTAGATA TTTTAAATAA TTCAAAATTT AATAAAAGAT GGAAGAGTTA 300
 TGGAACCTCA GATAATATAG ATAAATATAT GTCTTTAATA AATAAACATA ATAATGAAGA 360
 AATGTTTAAAC AACAATTATC AATCATTITT ATCGACAAGT TCATTAATAA AGCAAAATAA 420
 ATATGTTTCT ATTAACGCTG TACGTGTGTC TAGGATATTA AGTTTCCTGG ATTCTAGAAT 480
 TAATAATGGA AGAAATACTT CATCTAATAA CGAAGTTTGA AGTAATTGTA GGGAAAAAAG 540
 GAAAGGAATG AAATGGGATT GTAAAAAGAA AAATGATAGA AGCAACTATG TATGTATTCC 600
 TGATCGTAGA ATCCAATTAT GCATTGTTAA TCTTAGCATT ATTAACACAT ATACAAAAGA 660
 GACCATGAAG GATCATTTCA TTGAAGCCTC TAAAAAGAA TCTCACTTT TGCTTAAAAA 720
 AAATGATAAC AAATATAATT CTAAATTTTG TAATGATTTG AAGAATAGTT TTTTAGATTA 780

TGGACATCTT GCTATGGGAA ATGATATGGA TTTTGGAGGT TATTCAACTA AGGCAGAAAA 840
CAAAATTCAA GAAGTTTTTA AAGGGGCTCA TGGGGAAATA AGTGAACATA AAATTAAAAA 900
TTTTAGAAAA GAATGGTGGA ATGAATTTAG AGAGAACTT TGGGAAGCTA TGTTATCTGA 960
5 GCATAAAAAAT AATATAAATA ATTGTAAAAA TATTCCCCAA GAAGAATTAC AAATTACTCA 1020
ATGGATAAAA GAATGGCATG GAGAATTTTT GCTTGAAAGA GATAATAGAT CAAAATTGCC 1080
AAAAAGTAAA TGTA AAAATA ATACATTATA TGAAGCATGT GAGAAGGAAT GTATTGATCC 1140
ATGTATGAAA TATAGAGATT GGATTATTAG AAGTAAATTT GAATGGCATA CGTTATCGAA 1200
AGAATATGAA ACTCAAAAAG TTCCAAAGGA AAATGCGGAA AATTATTTAA TCAAAATTTT 1260
10 AGAAAACAAG AATGATGCTA AAGTAAGTTT ATTATTGAAT AATTGTGATG CTGAATATTC 1320
AAAATATTGT GATTGTAAAC ATACTACTAC TCTCGTTAAA AGCGTTTTAA ATGGTAACGA 1380
CAATACAATT AAGGAAAAGC GTGAACATAT TGATTTAGAT GATTTTTCTA AATTTGGATG 1440
TGATAAAAAAT TCCGTTGATA CAAACACAAA GGTGTGGGAA TGTA AAAACC CTTATATATT 1500
ATCCACTAAA GATGTATGTG TACCTCCGAG GAGGCAAGAA TTATGTCTTG GAAACATTGA 1560
TAGAATATAC GATAAAAACC TATTAATGAT AAAAGAGCAT ATTCTTGCTA TTGCAATATA 1620
15 TGAATCAAGA ATATTGAAAC GAAAATATAA GAATAAAGAT GATAAAGAAG TTTGTAAAT 1680
CATAAATAAA ACTTTCGCTG ATATAAGAGA TATTATAGGA GGTACTGATT ATTGGAATGA 1740
TTTGAGCAAT AGAAAATTAG TAGGAAAAAT TAACACAAAT TCAAAATATG TTCACAGGAA 1800
TAAAAAAAAT GATAAGCTTT TTCGTGATGA GTGGTGGAAA GTTATTA AAAA AAGATGTATG 1860
20 GAATGTGATA TCATGGGTAT TCAAGGATAA AACTGTTTGT AAAGAAGATG ATATTGAAAA 1920
TATACCACAA TTCTTCAGAT GGTTTAGTGA ATGGGGTGAT GATTATTGCC AGGATAAAAC 1980
AAAAATGATA GAGACTCTGA AGGTTGAATG CAAAGAAAAA CCTTGTGAAG ATGACAATTG 2040
TAAAAGTAAA TGTAATTCAT ATAAAGAATG GATATCAAAA AAAAAAGAAG AGTATAATAA 2100
ACAAGCCAAA CAATACCAAG AATATCAAAA AGGAAATAAT TACAAAATGT ATTCTGAATT 2160
TAAATCTATA AAACCAGAAG TTTATTTAAA GAAATACTCG GAAAAATGTT CTAACCTAAA 2220
25 TTTCTGAAGAT GAATTTAAGG AAGAATTACA TTCAGATTAT AAAAATAAAT GTACGATGTG 2280
TCCAGAAGTA AAGGATGTAC CAATTTCTAT AATAAGAAAT AATGAACAAA CTTGCAAGA 2340
AGCAGTTCCT GAGGAAAAACA CTGAAATAGC ACACAGAACG GAAACTCCAT CTATCTCTGA 2400
AGGACCAAAA GGAAATGAAC AAAAAGAACG TGATGACGAT AGTTTGAGTA AAATAAGTGT 2460
ATCACCAGAA AATTCAAGAC CTGAAACTGA TGCTAAAGAT ACTTCTAACT TGTAAAAATT 2520
30 AAAAGGAGAT GTTGATATTA GTTAGCCTAA AGCAGTTATT GGGAGCAGTC CTAATGATAA 2580
TATAAATGTT ACTGAACAAG GGGATAATAT TTCCGGGGTG AATTCTAAAC CTTTATCTGA 2640
TGATGTACGT CCAGATAAAA AGGAATTAGA AGATCAAAAT AGTGATGAAT CTTGAGAAAC 2700
TGTAAGTAAAT CATATATCAA AAAGTCCATC TATAAATAAT GGAGATGATT CAGGCAGTGG 2760
AAGTGCAACA GTGAGTGAAT CTAGTAGTTC AAATACTGGA TTGTCTATTG ATGATGATAG 2820
35 AAATGGTGAT ACATTTGTTC GAACACAAGA TACAGCAAAT ACTGAAGATG TTATTAGAAA 2880
AGAAAATGCT GACAAGGATG AAGATGAAAA AGGCGCAGAT GAAGAAAGAC ATAGTACTTC 2940
TGAAAGCTTA AGTTCACCTG AAGAAAAAAT GTTAACTGAT AATGAAGGAG GAAATGTTT 3000
AAATCATGAA GAGGTGAAAG AACATACTAG TAATTCTGAT AATGTTCAAC AGTCTGGAGG 3060
AATTGTTAAT ATGAATGTTG AGAAAGA ACT AAAAGATACT TTAGAAAATC CTTCTAGTAG 3120
40 CTTGGATGAA GGAAAAGCAC ATGAAGAATT ATCAGAACCA AATCTAAGCA GTGACCAAGA 3180
TATGTCTAAT ACACCTGGAC CTTTGGATAA CACCAGTGAA GAAACTACAG AAAGAATTAG 3240
TAATAATGAA TATAAAGTTA ACAGAGGGA AGATGAGAGA ACGCTTACTA AGGAATATGA 3300
AGATATTGTT TTGAAAAGTC ATATGAATAG AGAATCAGAC GATGGTGAAT TATATGACGA 3360
AAATTCAGAC TTATCTACTG TAAATGATGA ATCAGAAGAC GCTGAAGCAA AAATGAAAGG 3420
45 AAATGATACA TCTGAAATGT CGCATAATAG TAGTCAACAT ATTGAGAGTG ATCAACAGAA 3480
AAACGATATG AAAACTGTTG GTGATTTGGG AACCACACAT GTACAAAACG AAATTAGTGT 3540
TCCTGTTACA GGAGAAATTG ATGAAAAATT AAGGGAAAGT AAAGAATCAA AAATTCATAA 3600
GGCTGAAGAG GAAAGATTAA GTCATACAGA TATACATAA ATTAATCCTG AAGATAGAAA 3660
TAGTAATACA TTACATTTAA AAGATATAAG AAATGAGGAA AACGAAAGAC ACTTA ACTAA 3720
50 TCAAAACATT AATATTAGTC AAGAAAGGGA TTTGCAAAA CATGGATTCC ATACCATGAA 3780
TAATCTACAT GGAGATGGAG TTTCCGAAAG AAGTCAAATT AATCATAGTC ATCATGGAAA 3840
CAGACAAGAT CGGGGGGGAA ATTCTGGGAA TGTTTTAAAT ATGAGATCTA ATAATAATAA 3900
TTTTAATAAT ATTCCAAGTA GATATAATTT ATATGATAAA AAATTAGATT TAGATCTTTA 3960
TGAAAACAGA AATGATAGTA CAACAAAAGA ATTAATAAAG AAATTAGCAG AAATAAATAA 4020
55 ATGTGAGAAC GAAATTTCTG TAAATATTG TGACCATATG ATTCATGAAG AAATCCCATT 4080
AAAAACATGC ACTAAAGAAA AAACAAGAAA TCTGTGTTGT CGAGTATCAG ATTACTGTAT 4140
GAGCTATTTT ACATATGATT CAGAGGAATA TTATAATTGT ACGAAAAGGG AATTGTATGA 4200
TCCATCTTAT ACATGTTTCA GAAAGGAGGC TTTTCAAGT ATGATATTCA AATTTTAAAT 4260
AACAATAAAA ATATATTATT ATTTTATATC TTACAAA ACT GCAAAAGTAA CAATAAAAAA 4320
60 AATTAATTTT TCATTAATTT TTTTCTTCTT TTTTCTTCTT TAGGTATGCC ATATTATGCA 4380
GGAGCAGGTG TGTTATTTAT TATATTGTTT ATTTTAGGTG CTTACAAGC CAAATATCAA 4440
AGGTTAGAAA AAATAAATAA AAATAAATT GAGAAGAATG TAAATTAAT ATAGAATTCG 4500
AGCTCGG 4507

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1435 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Plasmodium falciparum

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Met	Lys	Cys	Asn	Ile	Ser	Ile	Tyr	Phe	Phe	Ala	Ser	Phe	Phe	Val	Leu	1	5	10	15
Tyr	Phe	Ala	Lys	Ala	Arg	Asn	Glu	Tyr	Asp	Ile	Lys	Glu	Asn	Glu	Lys	20	25	30	
Phe	Leu	Asp	Val	Tyr	Lys	Glu	Lys	Phe	Asn	Glu	Leu	Asp	Lys	Lys	Lys	35	40	45	
Tyr	Gly	Asn	Val	Gln	Lys	Thr	Asp	Lys	Lys	Ile	Phe	Thr	Phe	Ile	Glu	50	55	60	
Asn	Lys	Leu	Asp	Ile	Leu	Asn	Asn	Ser	Lys	Phe	Asn	Lys	Arg	Trp	Lys	65	70	75	80
Ser	Tyr	Gly	Thr	Pro	Asp	Asn	Ile	Asp	Lys	Asn	Met	Ser	Leu	Ile	Asn	85	90	95	
Lys	His	Asn	Asn	Glu	Glu	Met	Phe	Asn	Asn	Asn	Tyr	Gln	Ser	Phe	Leu	100	105	110	
Ser	Thr	Ser	Ser	Leu	Ile	Lys	Gln	Asn	Lys	Tyr	Val	Pro	Ile	Asn	Ala	115	120	125	
Val	Arg	Val	Ser	Arg	Ile	Leu	Ser	Phe	Leu	Asp	Ser	Arg	Ile	Asn	Asn	130	135	140	
Gly	Arg	Asn	Thr	Ser	Ser	Asn	Asn	Glu	Val	Leu	Ser	Asn	Cys	Arg	Glu	145	150	155	160
Lys	Arg	Lys	Gly	Met	Lys	Trp	Asp	Cys	Lys	Lys	Lys	Asn	Asp	Arg	Ser	165	170	175	
Asn	Tyr	Val	Cys	Ile	Pro	Asp	Arg	Arg	Ile	Gln	Leu	Cys	Ile	Val	Asn	180	185	190	
Leu	Ser	Ile	Ile	Lys	Thr	Tyr	Thr	Lys	Glu	Thr	Met	Lys	Asp	His	Phe	195	200	205	
Ile	Glu	Ala	Ser	Lys	Lys	Glu	Ser	Gln	Leu	Leu	Leu	Lys	Lys	Asn	Asp	210	215	220	
Asn	Lys	Tyr	Asn	Ser	Lys	Phe	Cys	Asn	Asp	Leu	Lys	Asn	Ser	Phe	Leu	225	230	235	240
Asp	Tyr	Gly	His	Leu	Ala	Met	Gly	Asn	Asp	Met	Asp	Phe	Gly	Gly	Tyr	245	250	255	
Ser	Thr	Lys	Ala	Glu	Asn	Lys	Ile	Gln	Glu	Val	Phe	Lys	Gly	Ala	His	260	265	270	
Gly	Glu	Ile	Ser	Glu	His	Lys	Ile	Lys	Asn	Phe	Arg	Lys	Glu	Trp	Trp	275	280	285	
Asn	Glu	Phe	Arg	Glu	Lys	Leu	Trp	Glu	Ala	Met	Leu	Ser	Glu	His	Lys	290	295	300	
Asn	Asn	Ile	Asn	Asn	Cys	Lys	Asn	Ile	Pro	Gln	Glu	Glu	Leu	Gln	Ile	305	310	315	320
Thr	Gln	Trp	Ile	Lys	Glu	Trp	His	Gly	Glu	Phe	Leu	Leu	Glu	Arg	Asp	325	330	335	
Asn	Arg	Ser	Lys	Leu	Pro	Lys	Ser	Lys	Cys	Lys	Asn	Asn	Thr	Leu	Tyr	340	345	350	
Glu	Ala	Cys	Glu	Lys	Glu	Cys	Ile	Asp	Pro	Cys	Met	Lys	Tyr	Arg	Asp	355	360	365	
Trp	Ile	Ile	Arg	Ser	Lys	Phe	Glu	Trp	His	Thr	Leu	Ser	Lys	Glu	Tyr				

[illegible]

				885					890					895			
	Asp	Asp	Ser	Gly	Ser	Gly	Ser	Ala	Thr	Val	Ser	Glu	Ser	Ser	Ser	Ser	Ser
				900						905				910			
5	Asn	Thr	Gly	Leu	Ser	Ile	Asp	Asp	Asp	Arg	Asn	Gly	Asp	Thr	Phe	Val	
			915					920					925				
	Arg	Thr	Gln	Asp	Thr	Ala	Asn	Thr	Glu	Asp	Val	Ile	Arg	Lys	Glu	Asn	
			930				935					940					
	Ala	Asp	Lys	Asp	Glu	Asp	Glu	Lys	Gly	Ala	Asp	Glu	Glu	Arg	His	Ser	
	945					950				955					960		
10	Thr	Ser	Glu	Ser	Leu	Ser	Ser	Pro	Glu	Glu	Lys	Met	Leu	Thr	Asp	Asn	
				965						970					975		
	Glu	Gly	Gly	Asn	Ser	Leu	Asn	His	Glu	Glu	Val	Lys	Glu	His	Thr	Ser	
				980					985					990			
	Asn	Ser	Asp	Asn	Val	Gln	Gln	Ser	Gly	Gly	Ile	Val	Asn	Met	Asn	Val	
15			995					1000				1005					
	Glu	Lys	Glu	Leu	Lys	Asp	Thr	Leu	Glu	Asn	Pro	Ser	Ser	Ser	Leu	Asp	
	1010						1015				1020						
	Glu	Gly	Lys	Ala	His	Glu	Glu	Leu	Ser	Glu	Pro	Asn	Leu	Ser	Ser	Asp	
	1025					1030					1035					1040	
20	Gln	Asp	Met	Ser	Asn	Thr	Pro	Gly	Pro	Leu	Asp	Asn	Thr	Ser	Glu	Glu	
				1045						1050					1055		
	Thr	Thr	Glu	Arg	Ile	Ser	Asn	Asn	Glu	Tyr	Lys	Val	Asn	Glu	Arg	Glu	
			1060						1065					1070			
	Asp	Glu	Arg	Thr	Leu	Thr	Lys	Glu	Tyr	Glu	Asp	Ile	Val	Leu	Lys	Ser	
25			1075					1080					1085				
	His	Met	Asn	Arg	Glu	Ser	Asp	Asp	Gly	Glu	Leu	Tyr	Asp	Glu	Asn	Ser	
	1090						1095					1100					
	Asp	Leu	Ser	Thr	Val	Asn	Asp	Glu	Ser	Glu	Asp	Ala	Glu	Ala	Lys	Met	
	1105					1110					1115					1120	
30	Lys	Gly	Asn	Asp	Thr	Ser	Glu	Met	Ser	His	Asn	Ser	Ser	Gln	His	Ile	
				1125						1130					1135		
	Glu	Ser	Asp	Gln	Gln	Lys	Asn	Asp	Met	Lys	Thr	Val	Gly	Asp	Leu	Gly	
			1140					1145					1150				
35	Thr	Thr	His	Val	Gln	Asn	Glu	Ile	Ser	Val	Pro	Val	Thr	Gly	Glu	Ile	
			1155					1160					1165				
	Asp	Glu	Lys	Leu	Arg	Glu	Ser	Lys	Glu	Ser	Lys	Ile	His	Lys	Ala	Glu	
	1170						1175					1180					
	Glu	Glu	Arg	Leu	Ser	His	Thr	Asp	Ile	His	Lys	Ile	Asn	Pro	Glu	Asp	
	1185					1190					1195					1200	
40	Arg	Asn	Ser	Asn	Thr	Leu	His	Leu	Lys	Asp	Ile	Arg	Asn	Glu	Glu	Asn	
				1205						1210					1215		
	Glu	Arg	His	Leu	Thr	Asn	Gln	Asn	Ile	Asn	Ile	Ser	Gln	Glu	Arg	Asp	
			1220					1225					1230				
45	Leu	Gln	Lys	His	Gly	Phe	His	Thr	Met	Asn	Asn	Leu	His	Gly	Asp	Gly	
			1235					1240					1245				
	Val	Ser	Glu	Arg	Ser	Gln	Ile	Asn	His	Ser	His	His	Gly	Asn	Arg	Gln	
			1250				1255					1260					
	Asp	Arg	Gly	Gly	Asn	Ser	Gly	Asn	Val	Leu	Asn	Met	Arg	Ser	Asn	Asn	
	1265					1270					1275					1280	
50	Asn	Asn	Phe	Asn	Asn	Ile	Pro	Ser	Arg	Tyr	Asn	Leu	Tyr	Asp	Lys	Lys	
				1285						1290					1295		
	Leu	Asp	Leu	Asp	Leu	Tyr	Glu	Asn	Arg	Asn	Asp	Ser	Thr	Thr	Lys	Glu	
			1300					1305						1310			
55	Leu	Ile	Lys	Lys	Leu	Ala	Glu	Ile	Asn	Lys	Cys	Glu	Asn	Glu	Ile	Ser	
			1315					1320					1325				
	Val	Lys	Tyr	Cys	Asp	His	Met	Ile	His	Glu	Glu	Ile	Pro	Leu	Lys	Thr	
			1330				1335					1340					
	Cys	Thr	Lys	Glu	Lys	Thr	Arg	Asn	Leu	Cys	Cys	Ala	Val	Ser	Asp	Tyr	
	1345					1350					1355					1360	
60	Cys	Met	Ser	Tyr	Phe	Thr	Tyr	Asp	Ser	Glu	Glu	Tyr	Tyr	Asn	Cys	Thr	
				1365						1370					1375		
	Lys	Arg	Glu	Phe	Asp	Asp	Pro	Ser	Tyr	Thr	Cys	Phe	Arg	Lys	Glu	Ala	
				1380				1385					1390				
	Phe	Ser	Ser	Met	Ile	Phe	Lys	Phe	Leu	Ile	Thr	Asn	Lys	Ile	Tyr	Tyr	

1395 1400 1405
Tyr Phe Tyr Thr Tyr Lys Thr Ala Lys Val Thr Ile Lys Lys Ile Asn
1410 1415 1420
Phe Ser Leu Ile Phe Phe Phe Phe Ser Phe
1425 1430 1435

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2288 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Plasmodium falciparum

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

CACTTTATGC TTCCGGCTCG TATGTTGTGT GGAATTGTGA GCGGATAACA ATTTACACACA 60
GGAAACAGCT ATGACCATGA TTACGCCAAG CTCTAATACG ACTCACTATA GGGAAAGCTG 120
GTACGCCTGC AGGTCCGGTC CGGAATTCAA TAAATATTTT CCAGAAAGGA ATGTGCAAAT 180
TCACATATCC AATATATTCA AGGAATATAA AGAAAATAAT GTAGATATCA TATTTGGAAC 240
GTTGAATTAT GAATATAATA ATTTCTGTAA AGAAAAACCT GAATTAGTAT CTGCTGCCAA 300
GTATAATCTG AAAGCTCCAA ATGCTAAATC CCCTAGAATA TACAAATCTA AGGAGCATGA 360
AGAATCAAGT GTGTTTGGTT GCAAAACGAA AATCAGTAAA GTTAAAAAAA AATGGAATTG 420
TTATAGTAAT AATAAAGTAA CTAAACCTGA AGGTGTATGT GGACCACCAA GAAGGCAACA 480
ATTATGTCTT GGATATATAT TTTTGATTCT CGACGGTAAC GAGGAAGGAT TAAAAGATCA 540
TATTAATAAG GCAGCTAATT ATGAGGCAAT GCATTTAAAA GAGAAATATG AGAATGCTGG 600
TGGTGATAAA ATTTGCAATG CTATATTGGG AAGTTATGCA GATATTGGAG ATATTGTAAG 660
AGGTTTGGAT GTTTGGAGGG ATATAAATAC TAATAAATTA TCAGAAAAAT TCCAAAAAAT 720
TTTTATGGGT GGTGGTAATT CTAGGAAAAA ACAAAACGAT AATAATGAAC GTAATAAATG 780
GTGGGAAAAA CAAAGGAATT TAATATGGTC TAGTATGGTA AAACACATTC CAAAAGGAAA 840
AACATGTAAA CGTCATAATA ATTTTGAGAA AATTCCTCAA TTTTGGAGAT GGTAAAAAGA 900
ATGGGGTGAT GAATTTTGTG AGGAAATGGG TACGGAAGTC AAGCAATTAG AGAAAATATG 960
TGAAAATAAA AATTGTTTCG AAAAAAATG TAAAAATGCA TGAGTTTCCT ATGAAAAATG 1020
GATAAAGGAA CGAAAAAATG ATATAATTT GCAATCAAAG AAATTTGATA GTGATAAAAA 1080
ATTAATAAAA AAAACAATC TTTATAATAA ATTTGAGGAT TCTAAAGCTT ATTTAAGGAG 1140
TGAATCAAAA CAGTGCTCAA ATATAGAATT TAATGATGAA ACATTTACAT TTCCTAATAA 1200
ATATAAGAGG GCTTGATATG TATGTGAAAA TCCTTCATCT TCGAAAGCTC TTAACCTAT 1260
AAAAACGAAT GTGTTTCCTA TAGAGGAATC AAAAAAATCT GAGTTATCAA GTTTAACAGA 1320
TAAATCTAAG AATACTCCTA ATAGTTCTGG TGGGGGAAAT TATGGAGATA GACAAATATC 1380
AAAAAGAGAC GATGTTTCATC ATGATGGTCC TAAGGAAGTG AAATCCGGAG AAAAAGAGGT 1440
ACCAAAAATA GATGCAGCTG TTAACACAGA AAATGAATTT ACCTCTAATC GAAACGATAT 1500
TGAAGGAAAG GAAAAAAGTA AAGGTGATCA TTCTTCTCCT GTTCATTCTA AAGATATAAA 1560
AAATGAGGAA CCACAAAGGG TGGTGTCTGA AAATTTACCT AAAATTGAAG AGAAAATGGA 1620
ATCTTCTGAT TCTATACCAA TTAATCATAT AGAAGCTGAA AAGGGTCAGT CTTCTAATTC 1680
TAGCGATAAT GATCCTGCAG TAGTAAGTGG TAGAGAATCT AAAGATGTAA ATCTTCATAC 1740
TTCTGAAAGG ATTAAGAAA ATGAAGAAGG TGTGATTAAA ACAGATGATA GTTCAAAAAG 1800
TATTGAAATT TCTAAATAC CATCTGACCA AAATAATCAT AGTGATTTAT CACAGAATGC 1860
AAATGAGGAC TCTAATCAAG GGAATAAGGA AACAATAAAT CCTCCTTCTA CAGAAAAAAA 1920
TCTCAAAGAA ATTCATTATA AAACATCTGA TTCTGATGAT CATGGTTCTA AGATAAAAAG 1980
TGAAATTGAA CCAAAGGAGT TAACGGAGGA ATCACCTCTT ACTGATAAAA AAACCTGAAAG 2040
TGCAGCGATT GGTGATAAAA ATCATGAATC AGTAAAAAGC GCTGATATTT TTCAATCTGA 2100
GATTCATAAT TCTGATAATA GAGATAGAAT TGTTTCTGAA AGTGTAGTTC AGGATTCCTC 2160
AGGAAGCTCT ATGAGTACTG AATCTATACG TACTGATAAC AAGGATTTTA AAACAAGTGA 2220
GGATATTGCA CCTTCTATTA ATGGTCGGAA TTCCCGGGTC GACGAGCTCA CTAGTCGGCG 2280
GCCGCTCT 2288

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 749 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

(A) ORGANISM: *Plasmodium falciparum*

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Ala Asp Asn Asn Phe Thr Gln Glu Thr Ala Met Thr Met Ile Thr Pro
 1 5 10 15
 Ser Ser Asn Thr Thr His Tyr Arg Glu Ser Trp Tyr Ala Cys Arg Ser
 20 25 30
 Gly Pro Glu Phe Asn Lys Ile Phe Pro Glu Arg Asn Val Gln Ile His
 35 40 45
 Ile Ser Asn Ile Phe Lys Glu Tyr Lys Glu Asn Asn Val Asp Ile Ile
 50 55 60
 Phe Gly Thr Leu Asn Tyr Glu Tyr Asn Asn Phe Cys Lys Glu Lys Pro
 65 70 75 80
 Glu Leu Val Ser Ala Lys Tyr Asn Leu Lys Ala Pro Asn Ala Lys
 85 90 95
 Ser Pro Arg Ile Tyr Lys Ser Lys Glu His Glu Glu Ser Ser Val Phe
 100 105 110
 Gly Cys Lys Thr Lys Ile Ser Lys Val Lys Lys Lys Trp Asn Cys Tyr
 115 120 125
 Ser Asn Asn Lys Val Thr Lys Pro Glu Gly Val Cys Gly Pro Pro Arg
 130 135 140
 Arg Gln Gln Leu Cys Leu Gly Tyr Ile Phe Leu Ile Arg Asp Gly Asn
 145 150 155 160
 Glu Glu Gly Leu Lys Asp His Ile Asn Lys Ala Ala Asn Tyr Glu Ala
 165 170 175
 Met His Leu Lys Glu Lys Tyr Glu Asn Ala Gly Gly Asp Lys Ile Cys
 180 185 190
 Asn Ala Ile Leu Gly Ser Tyr Ala Asp Ile Gly Asp Ile Val Arg Gly
 195 200 205
 Leu Asp Val Trp Arg Asp Ile Asn Thr Asn Lys Leu Ser Glu Lys Phe
 210 215 220
 Gln Lys Ile Phe Met Gly Gly Gly Asn Ser Arg Lys Lys Gln Asn Asp
 225 230 235 240
 Asn Asn Glu Arg Asn Lys Trp Trp Glu Lys Gln Arg Asn Leu Ile Trp
 245 250 255
 Ser Ser Met Val Lys His Ile Pro Lys Gly Lys Thr Cys Lys Arg His
 260 265 270
 Asn Asn Phe Glu Lys Ile Pro Gln Phe Leu Arg Trp Leu Lys Glu Trp
 275 280 285
 Gly Asp Glu Phe Cys Glu Glu Met Gly Thr Glu Val Lys Gln Leu Glu
 290 295 300
 Lys Ile Cys Glu Asn Lys Asn Cys Ser Glu Lys Lys Cys Lys Asn Ala
 305 310 315 320
 Cys Ser Ser Tyr Glu Lys Trp Ile Lys Glu Arg Lys Asn Glu Tyr Asn
 325 330 335
 Leu Gln Ser Lys Lys Phe Asp Ser Asp Lys Lys Leu Asn Lys Lys Asn
 340 345 350
 Asn Leu Tyr Asn Lys Phe Glu Asp Ser Lys Ala Tyr Leu Arg Ser Glu
 355 360 365
 Ser Lys Gln Cys Ser Asn Ile Glu Phe Asn Asp Glu Thr Phe Thr Phe

370 375 380
 Pro Asn Lys Tyr Lys Glu Ala Cys Met Val Cys Glu Asn Pro Ser Ser
 385 390 395 400
 5 Ser Lys Ala Leu Lys Pro Ile Lys Thr Asn Val Phe Pro Ile Glu Glu
 405 410 415
 Ser Lys Lys Ser Glu Leu Ser Ser Leu Thr Asp Lys Ser Lys Asn Thr
 420 425 430
 Pro Asn Ser Ser Gly Gly Gly Asn Tyr Gly Asp Arg Gln Ile Ser Lys
 435 440 445
 10 Arg Asp Asp Val His His Asp Gly Pro Lys Glu Val Lys Ser Gly Glu
 450 455 460
 Lys Glu Val Pro Lys Ile Asp Ala Ala Val Lys Thr Glu Asn Glu Phe
 465 470 475 480
 15 Thr Ser Asn Arg Asn Asp Ile Glu Gly Lys Glu Lys Ser Lys Gly Asp
 485 490 495
 His Ser Ser Pro Val His Ser Lys Asp Ile Lys Asn Glu Glu Pro Gln
 500 505 510
 Arg Val Val Ser Glu Asn Leu Pro Lys Ile Glu Glu Lys Met Glu Ser
 515 520 525
 20 Ser Asp Ser Ile Pro Ile Thr His Ile Glu Ala Glu Lys Gly Gln Ser
 530 535 540
 Ser Asn Ser Ser Asp Asn Asp Pro Ala Val Val Ser Gly Arg Glu Ser
 545 550 555 560
 25 Lys Asp Val Asn Leu His Thr Ser Glu Arg Ile Lys Glu Asn Glu Glu
 565 570 575
 Gly Val Ile Lys Thr Asp Asp Ser Ser Lys Ser Ile Glu Ile Ser Lys
 580 585 590
 Ile Pro Ser Asp Gln Asn Asn His Ser Asp Leu Ser Gln Asn Ala Asn
 595 600 605
 30 Glu Asp Ser Asn Gln Gly Asn Lys Glu Thr Ile Asn Pro Pro Ser Thr
 610 615 620
 Glu Lys Asn Leu Lys Glu Ile His Tyr Lys Thr Ser Asp Ser Asp Asp
 625 630 635 640
 35 His Gly Ser Lys Ile Lys Ser Glu Ile Glu Pro Lys Glu Leu Thr Glu
 645 650 655
 Glu Ser Pro Leu Thr Asp Lys Lys Thr Glu Ser Ala Ala Ile Gly Asp
 660 665 670
 Lys Asn His Glu Ser Val Lys Ser Ala Asp Ile Phe Gln Ser Glu Ile
 675 680 685
 40 His Asn Ser Asp Asn Arg Asp Arg Ile Val Ser Glu Ser Val Val Gln
 690 695 700
 Asp Ser Ser Gly Ser Ser Met Ser Thr Glu Ser Ile Arg Thr Asp Asn
 705 710 715 720
 45 Lys Asp Phe Lys Thr Ser Glu Asp Ile Ala Pro Ser Ile Asn Gly Arg
 725 730 735
 Asn Ser Arg Val Asp Glu Leu Thr Ser Arg Arg Pro Leu
 740 745

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2606 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Plasmodium falciparum

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

AGCTCTATTA CGACTCACTA TAGGGAAAGC TGGTACGCCT GCAGGTACCG GTCCGGAATT 60
 CCCGGGTCGA CGAGCTCACT AGTCGGCGGC CGCTCTAGAG GATCCAAGCT TAATAGTGTT 120
 TATACGTCTA TTGGCTTATT TTTAAATAGC TTAAAAAGCG GACCATGTAA AAAGGATAAT 180
 GATAATGCAG AGGATAATAT AGATTTTGGT GATGAAGGTA AAACATTTAA AGAGGCAGAT 240
 5 AATTGTAAAC CATGTTCTCA ATTTACTGTT GATTGTAAAA ATTGTAATGG TGGTGATACA 300
 AAAGGGAAGT GCAATGGCAG CAATGGCAAA AAGAATGGAA ATGATTATAT TACTGCAAGT 360
 GATATTGAAA ATGGAGGGAA TTCTATTGGA AATATAGATA TGGTTGTTAG TGATAAGGAT 420
 GCAAATGGAT TTAATGGTTT AGACGCTTGT GGAAGTGCAA ATATCTTTAA AGGTATTAGA 480
 AAAGAACAAT GGAAATGTGC TAAAGTATGT GGTTTAGATG TATGTGGTCT TAAAAATGGT 540
 10 AATGGTAGTA TAGATAAAGA TCAAAAACAA ATTATAATTA TTAGAGCATT GCTTAAACGT 600
 TGGGTAGAAT ATTTTTTAGA AGATTATAAT AAAATAATG CCAAAATTTT ACATTGTACG 660
 AAAAAGGATA ATGAATCCAC ATGTACAAAT GATTGTCCAA ATAAATGTAC ATGTGTAGAA 720
 GAGTGGATAA ATCAGAAAAG GACAGAATGG AAAAATATAA AAAAACATTA CAAAACACAA 780
 AATGAAAATG GTGACAATAA CATGAAATCT TTGGTTACAG ATATTTTGGG TGCCTTGCAA 840
 15 CCCCAAAGTG ATGTTAACAA AGCTATAAAA CTTGTAGTG GTTTAACTGC GTTCGAGAGT 900
 TTTTGTGGTC TTAATGGCGC TGATAACTCA GAAAAAAAG AAGGTGAAGA TTACGATCTT 960
 GTTCTATGTA TGCTTAAAAA TCTTGAAAAA CAAATTCAGG AGTGCAAAA GAAACATGGC 1020
 GAAACTAGTG TCGAAAATGG TGGCAAAATCA TGTACCCCCC TTGACAACAC CACCCTTGAG 1080
 GAGGAACCCA TAGAAGAGGA AAACCAAGTG GAAGCGCCGA ACATTTGTCC AAAACAAACA 1140
 20 GTGGAAGATA AAAAAAAGA GGAAGAAGAA GAAACTTGTA CACCGGCATC ACCAGTACCA 1200
 GAAAAACCGG TACCTCATGT GGCACGTTGG CGAACATTTA CACCACCTGA GGTATTCAAG 1260
 ATATGGAGGG GAAGGAGAAA TAAAACTACG TGCAGAAATAG TGGCAGAAAT GCTTAAAGAT 1320
 AAGAATGGAA GGACTACAGT AGGTGAATGT TATAGAAAAG AAACCTTATC TGAATGGACG 1380
 TGTGATGAAA GTAAGATTAA AATGGGACAG CATGGAGCAT GTATTCCTCC AAGAAGACAA 1440
 25 AAATTATGTT TACATTATTT AGAAAAATA ATGACAAATA CAAATGAATT GAAATACGCA 1500
 TTTATTAAAT GTGCTGCAGC AGAACTTTT TTGTTATGGC AAAACTACAA AAAAGATAAG 1560
 AATGGTAATG CAGAAGATCT CGATGAAAAA TTAAGAGGTG GTATTATCCC CGAAGATTTT 1620
 AAACGGCAAA TGTTCTATAC GTTTGCAGAT TATAGAGATA TATGTTTGGG TACGGATATA 1680
 TCATCAAAAA AAGATACAAG TAAAGGTGTA GGTAAAGTAA AATGCAATAT TGATGATGTT 1740
 30 TTTTATAAAA TTAGCAATAG TATTCGTTAC CGTAAAAGTT GGTGGGAAAC AAATGGTCCA 1800
 GTTATATGGG AAGGAATGTT ATGCGCTTTA AGTTATGATA CGAGCCTAAA TAATGTTAAT 1860
 CCGGAAACTC ACAAAAAACT TACCGAAGGC AATAACAACCT TTGAGAAAGT CATATTTGGT 1920
 AGTGATAGTA GCACTACTTT GTCCAAATTT TCTGAAAGAC CTCAATTTCT AAGATGGTTG 1980
 ACTGAATGGG GAGAAAATTT CTGCAAAGAA CAAAAAAGG AGTATAAGGT GTTGTGGCA 2040
 35 AAATGTAAGG ATTGTGATGT TGATGGTGAT GGTAAATGTA ATGGAAAATG TGTGCGTGC 2100
 AAAGATCAAT GTAAACAATA TCATAGTTGG ATTGGAATAT GGATAGATAA TTATAAAAAA 2160
 CAAAAAGGAA GATATACTGA GGTAAAAAAA ATACCTCTGT ATAAAGAAGA TAAAGACGTG 2220
 AAAAATCAG ATGATGCTCG CGATTATTTA AAAACACAAT TACAAAATAT GAAATGTGTA 2280
 AATGGAATA CTGATGAAAA TTGTGAGTAT AAGTGTATGC ATAAAACCTC ATCCACAAAT 2340
 40 AGTGATATGC CCGAATCGTT GGACGAAAAG CCGGAAAAGG TCAAAGACAA GTGTAATTGT 2400
 GTACCTAATG AATGCAATGC ATTGAGTGTA AGTGGTAGCG GTTTTCCTGA TGGTCAAGCT 2460
 TACGTACGCG TGCATGCGAC GTCATAGCTC TTCTATAGTG TCACCTAAAT TCAATTCACT 2520
 GGCCGTCGTT TTACAACGTC GTGACTGGGA AAACCTGGCG TTACCCAACCT TAATCGCCTT 2580
 GCAGCACATC CCCCTTTCGC CAGCTG 2606

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 921 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: *Plasmodium falciparum*

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Lys Leu Asn Ser Val Tyr Thr Ser Ile Gly Leu Phe Leu Asn Ser Leu
 1 5 10 15

Lys Ser Gly Pro Cys Lys Lys Asp Asn Asp Asn Ala Glu Asp Asn Ile
 20 25 30
 Asp Phe Gly Asp Glu Gly Lys Thr Phe Lys Glu Ala Asp Asn Cys Lys
 35 40 45
 Pro Cys Ser Gln Phe Thr Val Asp Cys Lys Asn Cys Asn Gly Gly Asp
 50 55 60
 Thr Lys Gly Lys Cys Asn Gly Ser Asn Gly Lys Lys Asn Gly Asn Asp
 65 70 75 80
 Tyr Ile Thr Ala Ser Asp Ile Glu Asn Gly Gly Asn Ser Ile Gly Asn
 85 90 95
 Ile Asp Met Val Val Ser Asp Lys Asp Ala Asn Gly Phe Asn Gly Leu
 100 105 110
 Asp Ala Cys Gly Ser Ala Asn Ile Phe Lys Gly Ile Arg Lys Glu Gln
 115 120 125
 Trp Lys Cys Ala Lys Val Cys Gly Leu Asp Val Cys Gly Leu Lys Asn
 130 135 140
 Gly Asn Gly Ser Ile Asp Lys Asp Gln Lys Gln Ile Ile Ile Arg
 145 150 155 160
 Ala Leu Leu Lys Arg Trp Val Glu Tyr Phe Leu Glu Asp Tyr Asn Lys
 165 170 175
 Ile Asn Ala Lys Ile Ser His Cys Thr Lys Lys Asp Asn Glu Ser Thr
 180 185 190
 Cys Thr Asn Asp Cys Pro Asn Lys Cys Thr Cys Val Glu Glu Trp Ile
 195 200 205
 Asn Gln Lys Arg Thr Glu Trp Lys Asn Ile Lys Lys His Tyr Lys Thr
 210 215 220
 Gln Asn Glu Asn Gly Asp Asn Asn Met Lys Ser Leu Val Thr Asp Ile
 225 230 235 240
 Leu Gly Ala Leu Gln Pro Gln Ser Asp Val Asn Lys Ala Ile Lys Pro
 245 250 255
 Cys Ser Gly Leu Thr Ala Phe Glu Ser Phe Cys Gly Leu Asn Gly Ala
 260 265 270
 Asp Asn Ser Glu Lys Lys Glu Gly Glu Asp Tyr Asp Leu Val Leu Cys
 275 280 285
 Met Leu Lys Asn Leu Glu Lys Gln Ile Gln Glu Cys Lys Lys Lys His
 290 295 300
 Gly Glu Thr Ser Val Glu Asn Gly Gly Lys Ser Cys Thr Pro Leu Asp
 305 310 315 320
 Asn Thr Thr Leu Glu Glu Glu Pro Ile Glu Glu Glu Asn Gln Val Glu
 325 330 335
 Ala Pro Asn Ile Cys Pro Lys Gln Thr Val Glu Asp Lys Lys Lys Glu
 340 345 350
 Glu Glu Glu Glu Thr Cys Thr Pro Ala Ser Pro Val Pro Glu Lys Pro
 355 360 365
 Val Pro His Val Ala Arg Trp Arg Thr Phe Thr Pro Pro Glu Val Phe
 370 375 380
 Lys Ile Trp Arg Gly Arg Arg Asn Lys Thr Thr Cys Glu Ile Val Ala
 385 390 395 400
 Glu Met Leu Lys Asp Lys Asn Gly Arg Thr Thr Val Gly Glu Cys Tyr
 405 410 415
 Arg Lys Glu Thr Tyr Ser Glu Trp Thr Cys Asp Glu Ser Lys Ile Lys
 420 425 430
 Met Gly Gln His Gly Ala Cys Ile Pro Pro Arg Arg Gln Lys Leu Cys
 435 440 445
 Leu His Tyr Leu Glu Lys Ile Met Thr Asn Thr Asn Glu Leu Lys Tyr
 450 455 460
 Ala Phe Ile Lys Cys Ala Ala Ala Glu Thr Phe Leu Leu Trp Gln Asn
 465 470 475 480
 Tyr Lys Lys Asp Lys Asn Gly Asn Ala Glu Asp Leu Asp Glu Lys Leu
 485 490 495
 Lys Gly Gly Ile Ile Pro Glu Asp Phe Lys Arg Gln Met Phe Tyr Thr
 500 505 510
 Phe Ala Asp Tyr Arg Asp Ile Cys Leu Gly Thr Asp Ile Ser Ser Lys
 515 520 525

5 Lys Asp Thr Ser Lys Gly Val Gly Lys Val Lys Cys Asn Ile Asp Asp
 530 535 540
 Val Phe Tyr Lys Ile Ser Asn Ser Ile Arg Tyr Arg Lys Ser Trp Trp
 545 550 555 560
 Glu Thr Asn Gly Pro Val Ile Trp Glu Gly Met Leu Cys Ala Leu Ser
 565 570 575
 Tyr Asp Thr Ser Leu Asn Asn Val Asn Pro Glu Thr His Lys Lys Leu
 580 585 590
 10 Thr Glu Gly Asn Asn Asn Phe Glu Lys Val Ile Phe Gly Ser Asp Ser
 595 600 605
 Ser Thr Thr Leu Ser Lys Phe Ser Glu Arg Pro Gln Phe Leu Arg Trp
 610 615 620
 Leu Thr Glu Trp Gly Glu Asn Phe Cys Lys Glu Gln Lys Lys Glu Tyr
 625 630 635 640
 15 Lys Val Leu Leu Ala Lys Cys Lys Asp Cys Asp Val Asp Gly Asp Gly
 645 650 655
 Lys Cys Asn Gly Lys Cys Val Ala Cys Lys Asp Gln Cys Lys Gln Tyr
 660 665 670
 20 His Ser Trp Ile Gly Ile Trp Ile Asp Asn Tyr Lys Lys Gln Lys Gly
 675 680 685
 Arg Tyr Thr Glu Val Lys Lys Ile Pro Leu Tyr Lys Glu Asp Lys Asp
 690 695 700
 Val Lys Asn Ser Asp Asp Ala Arg Asp Tyr Leu Lys Thr Gln Leu Gln
 705 710 715 720
 25 Asn Met Lys Cys Val Asn Gly Thr Thr Asp Glu Asn Cys Glu Tyr Lys
 725 730 735
 Cys Met His Lys Thr Ser Ser Thr Asn Ser Asp Met Pro Glu Ser Leu
 740 745 750
 30 Asp Glu Lys Pro Glu Lys Val Lys Asp Lys Cys Asn Cys Val Pro Asn
 755 760 765
 Glu Cys Asn Ala Leu Ser Val Ser Gly Ser Gly Phe Pro Asp Gly Gln
 770 775 780
 Ala Phe Gly Gly Gly Val Leu Glu Gly Thr Cys Lys Gly Leu Gly Glu
 785 790 795 800
 35 Pro Lys Lys Lys Ile Glu Pro Pro Gln Tyr Asp Pro Thr Asn Asp Ile
 805 810 815
 Leu Lys Ser Thr Ile Pro Val Thr Ile Val Leu Ala Leu Gly Ser Ile
 820 825 830
 40 Ala Phe Leu Phe Met Lys Val Ile Tyr Ile Tyr Val Trp Tyr Ile Tyr
 835 840 845
 Met Leu Cys Val Gly Ala Leu Asp Thr Tyr Ile Cys Gly Cys Ile Cys
 850 855 860
 Ile Cys Ile Phe Ile Cys Val Ser Val Tyr Val Cys Val Tyr Val Tyr
 865 870 875 880
 45 Val Phe Leu Tyr Met Cys Val Phe Tyr Ile Tyr Phe Ile Tyr Ile Tyr
 885 890 895
 Val Phe Ile Leu Lys Met Lys Lys Met Lys Lys Met Lys Lys Met Lys
 900 905 910
 50 Lys Met Lys Lys Arg Lys Lys Arg Ile
 915 920

(2) INFORMATION FOR SEQ ID NO:9:

- 55 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 2101 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 60 (ii) MOLECULE TYPE: DNA (genomic)
 (iii) HYPOTHETICAL: NO
 (vi) ORIGINAL SOURCE:

(A) ORGANISM: *Plasmodium falciparum*

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

```

5  GGAACAGGGT GATAATAAAG TAGGAGCCTG TGCTCCGTAT AGACGATTAC ATTTATGTGA 60
   TTATAATTTG GAATCTATAG ACACAACGTC GACGACGCAT AAGTTGTTGT TAGAGGTGTG 120
   TATGGCAGCA AAATACGAAG GAAACTCAAT AAATACACAT TATACACAAC ATCAACGAAC 180
   TAATGAGGAT TCTGCTTCCC AATTATGTAC TGTATTAGCA CGAAGTTTTC CAGATATAGG 240
10  TGATATCGTA AGAGGAAAAG ATCTATATCT CGGTTATGAT AATAAAGAAA AAGAACAAG 300
   AAAAAAATTA GAACAGAAAT TGAAAGATAT TTTCAAGAAA ATACATAAGG ACGTGATGAA 360
   GACGAATGGC GCACAAGAAC GCTACATAGA TGATGCCAAA GGAGGAGATT TTTTCAATT 420
   AAGAGAAGAT TGGTGGACGT CGAATCGAGA AACAGTATGG AAAGCATTAA TATGTCATGC 480
   ACCAAAAGAA GCTAATTAT TTTATAAAAAC AGCGTGTAAT GTAGGAAAAG GAACTAATGG 540
   TCAATGCCAT TGCATTGGTG GAGATGTTCC CACATATTTT GATTATGTGC CGCAGTATCT 600
15  TCGCTGGTTC GAGGAATGGG CAGAAGACTT TTGCAGGAAA AAAAAAAAAA AACTAGAAAA 660
   TTTGCAAAAA CAGTGTCGTG ATTACGAACA AAATTTATAT TGTAGTGGTA ATGGCTACGA 720
   TTGCACAAAA ACTATATATA AAAAAGGTAA ACTTGTTATA GGTGAACATT GTACAAACTG 780
   TTCTGTTTTG TGTCGTATGT ATGAACTTG GATAGATAAC CAGAAAAAG AATTTCTAAA 840
   ACAAAAAAGA AAATACGAAA CAGAAATATC AGGTGGTGGT AGTGGTAAGA GTCCTAAAAG 900
20  GACAAAACGG GCTGCACGTA GTAGTAGTAG TAGTGATGAT AATGGGTATG AAAGTAAATT 960
   TTATAAAAAA CTGAAAGAAG TTGGCTACCA AGATGTCGAT AAATTTTAA AAATATTAAA 1020
   CAAAGAAGGA ATATGTCAAA AACAACCTCA AGTAGGAAAT GAAAAAGCAG ATAATGTTGA 1080
   TTTTACTAAT GAAAAATATG TAAAAACATT TTCTCGTACA GAAATTTGTG AACCGTGCCC 1140
   ATGGTGTGGA TTGGAAAAAG GTGGTCCACC ATGGAAAGTT AAAGGTGACA AAACCTGCGG 1200
25  AAGTGCAAAA ACAAAGACAT ACGATCCTAA AAATATTACC GATATACCAG TACTCTACCC 1260
   TGATAAATCA CAGCAAAATA TACTAAAAAA ATATAAAAAT TTTTGTGAAA AAGGTGCACC 1320
   TGGTGGTGGT CAAATTAAAA AATGGCAATG TTATTATGAT GAACATAGGC CTAGTAGTAA 1380
   AAATAATAAT AATTGTGTAG AAGGAACATG GGACAAGTTT ACACAAGGTA AACAAACCGT 1440
   TAAGTCCTAT AATGTTTTTT TTTGGGATTG GGTTTCATGAT ATGTTACACG ATTCTGTAGA 1500
30  GTGGAAGACA GAACTTAGTA AGTGATAA TAATAACACT AATGGCAACA CATGTAGAAA 1560
   CAATAATAAA TGTAAACAG ATTGTGGTTG TTTTCAAAA TGGGTTGAAA AAAAACAACA 1620
   AGAATGGATG GCAATAAAAG ACCATTTTGG AAAGCAACA GATATTGTCC AACAAAAAGG 1680
   TCTTATCGTA TTTAGTCCCT ATGGAGTTCT TGACCTTGTT TTGAAGGGCG GTAATCTGTT 1740
   GCAAAATATT AAAGATGTTT ATGGAGATAC AGATGACATA AAACACATTA AGAACTGTT 1800
35  GGATGAGGAA GACGCAGTAG CAGTTGTTCT TGGTGGCAAG GACAATACCA CAATTGATAA 1860
   ATTACTCAA CACGAAAAAG AACAGCAGA ACAATGCAA CAAAAGCAGG AAGAATGCGA 1920
   GAAAAAGCA CAACAAGAAA GTCGTGGTCG CTCCGCCGAA ACCCGCGAAG ACGAAAGGAC 1980
   ACAACAACCT GCTGATAGTG CCGGCGAAGT CGAAGAAGAA GAAGACGACG ACGACTACGA 2040
40  CGAAGACGAC GAAGATGACG ACGTAGTCCA GGACGTAGAT GTAAGTGAAA TAAGAGGTCC 2100
   G

```

(2) INFORMATION FOR SEQ ID NO:10:

```

45  (i) SEQUENCE CHARACTERISTICS:
      (A) LENGTH: 700 amino acids
      (B) TYPE: amino acid
      (C) STRANDEDNESS: single
      (D) TOPOLOGY: linear

```

```

50  (ii) MOLECULE TYPE: protein

```

```

      (iii) HYPOTHETICAL: NO

```

```

55  (vi) ORIGINAL SOURCE:
      (A) ORGANISM: Plasmodium falciparum

```

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

```

60  Glu Gln Gly Asp Asn Lys Val Gly Ala Cys Ala Pro Tyr Arg Arg Leu
     1           5           10           15
   His Leu Cys Asp Tyr Asn Leu Glu Ser Ile Asp Thr Thr Ser Thr Thr
     20           25           30
   His Lys Leu Leu Leu Glu Val Cys Met Ala Ala Lys Tyr Glu Gly Asn
     35           40           45

```


Ser Ile Asn Thr His Tyr Thr Gln His Gln Arg Thr Asn Glu Asp Ser
 50 55 60
 Ala Ser Gln Leu Cys Thr Val Leu Ala Arg Ser Phe Ala Asp Ile Gly
 65 70 75 80
 5 Asp Ile Val Arg Gly Lys Asp Leu Tyr Leu Gly Tyr Asp Asn Lys Glu
 85 90 95
 Lys Glu Gln Arg Lys Lys Leu Glu Gln Lys Leu Lys Asp Ile Phe Lys
 100 105 110
 10 Lys Ile His Lys Asp Val Met Lys Thr Asn Gly Ala Gln Glu Arg Tyr
 115 120 125
 Ile Asp Asp Ala Lys Gly Gly Asp Phe Phe Gln Leu Arg Glu Asp Trp
 130 135 140
 Trp Thr Ser Asn Arg Glu Thr Val Trp Lys Ala Leu Ile Cys His Ala
 145 150 155 160
 15 Pro Lys Glu Ala Asn Tyr Phe Ile Lys Thr Ala Cys Asn Val Gly Lys
 165 170 175
 Gly Thr Asn Gly Gln Cys His Cys Ile Gly Gly Asp Val Pro Thr Tyr
 180 185 190
 Phe Asp Tyr Val Pro Gln Tyr Leu Arg Trp Phe Glu Glu Trp Ala Glu
 195 200 205
 20 Asp Phe Cys Arg Lys Lys Lys Lys Lys Leu Glu Asn Leu Gln Lys Gln
 210 215 220
 Cys Arg Asp Tyr Glu Gln Asn Leu Tyr Cys Ser Gly Asn Gly Tyr Asp
 225 230 235 240
 25 Cys Thr Lys Thr Ile Tyr Lys Lys Gly Lys Leu Val Ile Gly Glu His
 245 250 255
 Cys Thr Asn Cys Ser Val Trp Cys Arg Met Tyr Glu Thr Trp Ile Asp
 260 265 270
 Asn Gln Lys Lys Glu Phe Leu Lys Gln Lys Arg Lys Tyr Glu Thr Glu
 275 280 285
 30 Ile Ser Gly Gly Gly Ser Gly Lys Ser Pro Lys Arg Thr Lys Arg Ala
 290 295 300
 Ala Arg Ser Ser Ser Ser Ser Asp Asp Asn Gly Tyr Glu Ser Lys Phe
 305 310 315 320
 35 Tyr Lys Lys Leu Lys Glu Val Gly Tyr Gln Asp Val Asp Lys Phe Leu
 325 330 335
 Lys Ile Leu Asn Lys Glu Gly Ile Cys Gln Lys Gln Pro Gln Val Gly
 340 345 350
 Asn Glu Lys Ala Asp Asn Val Asp Phe Thr Asn Glu Lys Tyr Val Lys
 355 360 365
 40 Thr Phe Ser Arg Thr Glu Ile Cys Glu Pro Cys Pro Trp Cys Gly Leu
 370 375 380
 Glu Lys Gly Gly Pro Pro Trp Lys Val Lys Gly Asp Lys Thr Cys Gly
 385 390 395 400
 45 Ser Ala Lys Thr Lys Thr Tyr Asp Pro Lys Asn Ile Thr Asp Ile Pro
 405 410 415
 Val Leu Tyr Pro Asp Lys Ser Gln Gln Asn Ile Leu Lys Lys Tyr Lys
 420 425 430
 Asn Phe Cys Glu Lys Gly Ala Pro Gly Gly Gly Gln Ile Lys Lys Trp
 435 440 445
 50 Gln Cys Tyr Tyr Asp Glu His Arg Pro Ser Ser Lys Asn Asn Asn Asn
 450 455 460
 Cys Val Glu Gly Thr Trp Asp Lys Phe Thr Gln Gly Lys Gln Thr Val
 465 470 475 480
 55 Lys Ser Tyr Asn Val Phe Phe Trp Asp Trp Val His Asp Met Leu His
 485 490 495
 Asp Ser Val Glu Trp Lys Thr Glu Leu Ser Lys Cys Ile Asn Asn Asn
 500 505 510
 Thr Asn Gly Asn Thr Cys Arg Asn Asn Lys Cys Lys Thr Asp Cys
 515 520 525
 60 Gly Cys Phe Gln Lys Trp Val Glu Lys Lys Gln Gln Glu Trp Met Ala
 530 535 540
 Ile Lys Asp His Phe Gly Lys Gln Thr Asp Ile Val Gln Gln Lys Gly
 545 550 555 560

5 Leu Ile Val Phe Ser Pro Tyr Gly Val Leu Asp Leu Val Leu Lys Gly
 Gly Asn Leu Leu Gln Asn Ile Lys Asp Val His Gly Asp Thr Asp Asp
 10 Ile Lys His Ile Lys Lys Leu Leu Asp Glu Glu Asp Ala Val Ala Val
 Val Leu Gly Gly Lys Asp Asn Thr Thr Ile Asp Lys Leu Leu Gln His
 Glu Lys Glu Gln Ala Glu Gln Cys Lys Gln Lys Gln Glu Glu Cys Glu
 15 Lys Lys Ala Gln Gln Glu Ser Arg Gly Arg Ser Ala Glu Thr Arg Glu
 Asp Glu Arg Thr Gln Gln Pro Ala Asp Ser Ala Gly Glu Val Glu Glu
 Glu Glu Asp Asp Asp Tyr Asp Glu Asp Asp Glu Asp Asp Val
 20 Val Gln Asp Val Asp Val Ser Glu Ile Arg Gly Pro
 565 570 575 580 585 590 595 600 605 610 615 620 625 630 635 640 645 650 655 660 665 670 675 680 685 690 695 700

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 8220 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

(A) ORGANISM: Plasmodium falciparum

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

AAAAATGGGG CCCAAGGAGG CTGCAGGTGG GGATGATATT GAGGATGAAA GTGCCAAACA 60
 TATGTTTGGAT AGGATAGGAA AAGATGTGTA CGATAAAGTA AAAGAGGAAG CTAAGAACG 120
 TGGTAAAGGC TTGCAAGGAC GTTTGTCAGA AGCAAAATTT GAGAAAAATG AAAGCGATCC 180
 40 ACAACACCA GAAGATCCAT GCGATCTTGA TCATAAATAT CATACAAATG TAACTACTAA 240
 TGTAATTAAT CCGTGCCTG ATAGATCTGA CGTGCGTTTT TCCGATGAAT ATGGAGGTCA 300
 ATGTACACAT AATAGAATAA AAGATAGTCA ACAGGGTGAT AATAAAGGTG CATGTGCTCC 360
 ATATAGGCGA TTGCATGTAT GCGATCAAAA TTAGAACAG ATAGAGCCTA TAAAAATAAC 420
 AAATACTCAT AATTTATTGG TAGATGTGTG TATGGCAGCA AAATTTGAAG GACAATCAAT 480
 45 AACACAAGAT TATCCAAAT ATCAAGCAAC ATATGGTGAT TCTCCTTCTC AAATATGTAC 540
 TATGCTGGCA CGAAGTTTTG CGGACATAGG GGACATTGTC AGAGGAAGAG ATTTGTATTT 600
 AGGTAATCCA CAAGAAATAA AACAAAGACA ACAATTAGAA AATAATTTGA AAACAATTTT 660
 CGGGAAAATA TATGAAAAAT TGAATGGCGC AGAAGCACGC TACGGAAATG ATCCGGAATT 720
 TTTTAAATTA CGAGAAGATT GGTGGACTGC TAATCGAGAA ACAGTATGGA AAGCCATCAC 780
 50 ATGTAACGCT TGGGGTAATA CATATTTTCA TGCAACGTGC AATAGAGGAG AACGAACATA 840
 AGGTTACTGC CCGTGTAACG ACGACCAAGT TCCCACATAT TTTGATTATG TGCCGCAGTA 900
 TCTTCGCTGG TTCGAGGAAT GGGCAGAAGA TTTTGTAGG AAAAAAATA AAAAAATAAA 960
 AGATGTTTAA AGAAATTGTC GTGGAAAAGA TAAAGAGGAT AAGGATCGAT ATTGTAGCCG 1020
 TAATGGCTAC GATTGCGAAA AACTAAACG AGCGATTGGT AAGTTGCGTT ATGGTAAGCA 1080
 55 ATGCATTAGC TGTTTGTATG CATGTAATCC TTACGTTGAT TGGATAAATA ACCAAAAAGA 1140
 ACAATTTGAC AAACAGAAAA AAAAATATGA TGAAGAAATA AAAAAATATG AAAATGGAGC 1200
 ATCAGGTGGT AGTAGGCAAA AACGGGATGC AGGTGGTACA ACTACTACTA ATTATGATGG 1260
 ATATGAAAAA AAATTTTATG ACGAACTTAA TAAAGTGAA TATAGAACCG TTGATAAATT 1320
 TTTGGAAAAA TTAAGTAATG AAGAAATATG CACAAAAGTT AAAGACGAAG AAGGAGGAAC 1380
 60 AATTGATTTT AAAAACGTTA ATAGTGATAG TACTAGTGGT GCTAGTGGCA CTAATGTTGA 1440
 AAGTCAAGGA ACATTTTATC GTTCAAAATA TTGCCAACCC TGCCCTTATT GTGGAGTGAA 1500
 AAAGGTAAAT AATGGTGGTA GTAGTAATGA TTGGGAAGAG AAAAATAATG GCAAGTGCAA 1560
 GAGTGGAAAA CTTTATGAGC CTAACCCGA CAAAGAAGGT ACTACTATTA CAATCCTTAA 1620
 AAGTGGTAAA GGACATGATG ATATTGAAGA AAAATTAAAC AAATTTTGTG ATGAAAAAAA 1680

	TGGTGATACA	ATAAATAGTG	GTGGTAGTGG	TACGGGTGGT	AGTGGTGGTG	GTAACAGTGG	1740
	TAGACAGGAA	TTGTATGAAG	AATGGAAATG	TTATAAAGGT	GAAGATGTAG	TGAAAGTTGG	1800
	ACACGATGAG	GATGACGAGG	AGGATTATGA	AAATGTAAAA	AATGCAGGCG	GATTATGTAT	1860
	ATTAAAAAAC	CAAAAAAAGA	ATAAAGAAGA	AGGTGGAAAT	ACGTCTGAAA	AGGAGCCTGA	1920
5	TGAAATCCAA	AAGACATTCA	ATCCTTTTTT	TTACTATTGG	GTTGCACATA	TGTTAAAAAGA	1980
	TTCCATACAT	TGGAAAAAAA	AACCTTCAGAG	ATGTTTACAA	AATGGTAACA	GAATAAAATG	2040
	TGGAAACAAT	AAATGTAATA	ATGATTGTGA	ATGTTTTTAA	AGATGGATTA	CACAAAAAAA	2100
	AGACGAATGG	GGGAAAATAG	TACAACATTT	TAAAACGCAA	AATATTAAAG	GTAGAGGAGG	2160
	TAGTGACAAT	ACGGCAGAAT	TAATCCCATT	TGATCACGAT	TATGTTCTTC	AATACAATTT	2220
10	GCAAGAAGAA	TTTTTGAAAG	GCGATTCCGA	AGACGCTTCC	GAAGAAAAAT	CCGAAAATAG	2280
	TCTGGATGCA	GAGGAGGCAG	AGGAACTAAA	ACACCTTCGC	GAAATCATTG	AAAGTGAAGA	2340
	CAATAATCAA	GAAGCATCTG	TTGGTGGTGG	CGTCACTGAA	CAAAAAAATA	TAATGGATAA	2400
	ATTGCTCAAC	TACGAAAAAG	ACGAAGCCGA	TTTATGCCTA	GAAATTCACG	AAGATGAGGA	2460
	AGAGGAAAAA	GAAAAAGGAG	ACGGAACCGA	ATGTATCGAA	GAGGGCGAAA	ATTTTCGTTA	2520
15	TAATCCATGT	AGTGGCGAAA	GTGGTAACAA	ACGATACCCC	GTTCTTGCGA	ACAAAGTAGC	2580
	GTATCAAATG	CATCACAAGG	CAAAGACACA	ATTGGCTAGT	CGTGCTGGTA	GAAGTGC GTT	2640
	GAGAGGTGAT	ATATCCTTAG	CGCAATTTAA	AAATGGTTCG	AACGGAAGTA	CATTGAAAGG	2700
	ACAAATTTGC	AAAATTAACG	AAAACATATC	CAATGTAGT	CGTGGTAATA	GTGGGATACC	2760
	ATGTACAGGC	AAAGATGGAG	ATCACGGAGG	TGTGCGCATG	AGAATAGGAA	CGGAATGGTC	2820
20	AAATATTGAA	GGAAAAA AAC	AAACGTCATA	CAAAAACGTC	TTTTTACCTC	CCCACGAGA	2880
	ACACATGTGT	ACATCCAATT	TAGAAAATTT	AGATGTTGGT	AGTGTCAC TA	AAAATGATAA	2940
	GGCTAGCCAC	TCATTATTGG	GAGATGTTCA	GCTCGCAGCA	AAAAC TGATG	CAGCTGAGAT	3000
	AATAAAACGC	TATAAAGATC	AAAATAATAT	ACAACTA ACT	GATCCAATAC	AACAAAAAGA	3060
	CCAGGAGGCT	ATGTGTCGAG	CTGTACGTTA	TAGTTTTGCC	GATTTAGGAG	ACATTATTCC	3120
25	AGGAAGAGAT	ATGTGGGATG	AGGATAAGAG	CTCAACAGAC	ATGGAAACAC	GTTTGATAAC	3180
	CGTATTTAAA	AACATTAAAG	AAAAACATGA	TGGAATCAAA	GACAACCCTA	AATATACCGG	3240
	TGATGAAAGC	AAAAAGCCCC	CATATAAAAA	ATTACGAGCA	GATTGGTGGG	AAGCAAATAG	3300
	ACATCAAGTG	TGGAGAGCCA	TGAAATGCGC	AACAAAAGGC	ATCATATGTC	CTGGTATGCC	3360
	AGTTGACGAT	TATATCCCCC	AACGTTTACG	CTGGATGACT	GAATGGGCTG	AATGGTATTG	3420
30	TAAAGCGCAA	TCACAGGAGT	ATGACAAGTT	AAAAAAATC	TGTGCAGATT	GTATGAGTAA	3480
	GGGTGATGGA	AAATGTACGC	AAGGTGATGT	CGATGTGGGA	AAGTGCAAAG	CAGCATGTGA	3540
	TAAATATAAA	GAGGAAATAG	AAAAATGGAA	TGAACAATGG	AGAAAAATAT	CAGATAAATA	3600
	CAATCTATTA	TACCTACAAG	CAAAA ACTAC	TTCTACTAAT	CCTGGCCGTA	CTGTTCTTGG	3660
	TGATGACGAT	CCCGACTATC	AACAAATGGT	AGATTTTTTG	ACCCCAATAC	ACAAAGCAAG	3720
35	TATTGCCGCA	CGTGTTCTTG	TTAAACGTGC	TGCTGGTAGT	CCCACTGAGA	TCGCCGCCGC	3780
	CGCCCCGATC	ACCCCCTACA	GTACTGTCTG	CGGATATATA	CACCAGGAAA	TAGGATATGG	3840
	GGGGTGCCAG	GAACAAACAC	AATTTTGTCG	AAAAAAACAT	GGTGCAACAT	CAACTAGTAC	3900
	CACGAAAGAA	AACAAAGAAT	ACACCTTTAA	ACAACTCCG	CCGGAGTATG	CAACATCGTG	3960
	TGATTGCATA	AATAGGTCGC	AAACAGAGGA	GCCGAAGAAA	AAGGAAGAAA	ATGTAGAGAG	4020
40	TGCCTGCAAA	ATAGTGAGAG	AAATACTTGA	GGGTAAGAAT	GGAAGGACTA	CAGTAGGTGA	4080
	ATGTAATCCA	AAAGAGAGTT	ATCCTGATTG	GGATTGCAAA	AACAATATTG	ACATTAGTCA	4140
	TGATGGTGTG	TGTATGCCTC	CAAGGAGACA	AAAAC TATGT	TTATATTATA	TAGCACATGA	4200
	GAGTCAAACT	GAAAATATAA	AAACAGACGA	TAATTTGAAA	GATGCTTTTA	TTAAAAC TGC	4260
	AGCAGCAGAA	ACTTTTCTTT	CATGGCAATA	TTATAAGAGT	AAGAATGATA	TTTGAAGCTAA	4320
45	AATATTAGAT	AGAGGCCTTA	TTCCATCCCA	ATTTTTTAAGA	TCCATGATGT	ACACGTTTGG	4380
	AGATTATAGA	GATATATGTT	TGAACACAGA	TATATCTAAA	AAACAAAATG	ATGTAGCTAA	4440
	GGCAAAAGAT	AAAATAGGTA	AATTTTTCTC	AAAAGATGGC	AGCAAATCTC	CTAGTGGCTT	4500
	ATCACGCCAA	GAATGGTGGA	AAACAAATGG	TCCAGAGATT	TGGAAAGGAA	TGTTATGTGC	4560
	CTTAACAAAA	TACGTCACAG	ATACCGATAA	CAAAAGAAAA	ATCAAAAACG	ACTACTCATA	4620
50	CGATAAAGTC	AACCAATCCC	AAAATGGCAA	CCCTTCCCTT	GAAGAGTTTG	CTGCTAAACC	4680
	TCAATTTCTA	CGTTGGATGA	TCGAATGGGG	AGAAGAGTTT	TGTGCTGAAC	GTCAGAAGAA	4740
	GGAAAATATC	ATAAAAGATG	CATGTAATGA	AATAAATTCT	ACACAACAGT	GTAATGATGC	4800
	GAAACATCGT	TGTAATCAAG	CATGTAGAGC	ATATCAAGAA	TATGTTGAAA	ATAAAAAAAA	4860
	AGAATTTTCG	GGACAAACAA	ATAACTTTGT	TCTAAAGGCA	AATGTTTCAGC	CCCAAGATCC	4920
55	AGAATATAAA	GGATATGAAT	ATAAAGACGG	CGTACAACCG	ATACAGGGGA	ATGAGTATTT	4980
	ACTGCAAAAA	TGTGATAATA	ATAAATGTTT	TTGATGGAT	GGAAATGTAC	TTTCCGTCTC	5040
	TCCAAAAGAA	AAACCTTTTG	GAAAATATGC	CCATAAATAT	CCTGAGAAAT	GTGATTGTTA	5100
	TCAAGGAAAA	CATGTACCTA	GCATACCACC	TCCCCCCCCA	CCTGTACAAC	CACAACCGGA	5160
	AGCACCAACA	GTAACAGTAG	ACGTTTGCAG	CATAGTAAAA	ACACTATTTA	AAGACACAAA	5220
60	CAATTTTTTC	GACGCTTGTG	GTCTAAAATA	CGGCAAAACC	GCACCATCCA	GTTGGAAATG	5280
	TATACCAAGT	GACACAAAAA	GTGGTGCTGG	TGCCACCACC	GGCAAAAGTG	GTAGTGATAG	5340
	TGGTAGTATT	TGTATCCAC	CCAGGAGGCG	ACGATTATAT	GTGGGGAAAC	TACAGGAGTG	5400
	GGCTACCGCG	CTCCCACAAG	GTGAGGGCGC	CGCGCCGTCC	CACTCACGCG	CCGACGACTT	5460
	GCGCAATGCG	TTCATCCAAT	CTGCTGCAAT	AGAGACTTTT	TTCTTATGGG	ATAGATATAA	5520

AGAAGAGAAA AAACCACAGG GTGATGGGTC ACAACAAGCA CTATCACAAC TAACCAGTAC 5580
 ATACAGTGAT GACGAGGAGG ACCCCCCCGA CAAACTGTTA CAAAATGGTA AGATACCCCC 5640
 CGATTTTTTG AGATTAATGT TCTATACATT AGGAGATTAT AGGGATATTT TAGTACACGG 5700
 TGGTAACACA AGTGACAGTG GTAACACAAA TGGTAGTAAC AACAACAATA TTGTGCTTGA 5760
 5 AGCGAGTGGT AACAAGGAGG ACATGCAAAA AATACAAGAG AAAATAGAAC AAATTCTCCC 5820
 AAAAAATGGT GGCACACCTC TTGTCCCAAA ATCTAGTGCC CAAACACCTG ATAAATGGTG 5880
 GAATGAACAC GCCGAATCTA TCTGGAAGG TATGATATGT GCATTGACAT ATACAGAAAA 5940
 GAACCCCTGAC ACCAGTGCAA GAGGCGACGA AAACAAAATA GAAAAGGATG ATGAAGTGTA 6000
 CGAGAAATTT TTTGGCAGCA CAGCCGACAA ACATGGCACA GCCTCAACCC CAACCGGCAC 6060
 10 ATACAAAACC CAATACGACT ACGAAAAAGT CAAACTTGAG GATACAAGTG GTGCCAAAAC 6120
 CCCCTCAGCC TCTAGTGATA CACCCCTTCT CTCCGATTTC GTGTTACGCC CCCCTACTT 6180
 CCGTTACCTT GAAGAATGGG GTCAAAATTT TTGTAAAAAA AGAAAGCATA AATTGGCACA 6240
 AATAAAACAT GAGTGTAAGT TAGAAGAAAA TGGTGGTGGT AGTCGTCGTG GTGGTATAAC 6300
 AAGACAATAT AGTGGGGATG GCGAAGCGTG TAATGAGATG CTTCCAAAAA ACGATGGAAC 6360
 15 TGTTCCGGAT TTAGAAAAGC CGAGTTGTGC CAAACCTTGT AGTTCTTATA GAAAATGGAT 6420
 AGAAAGCAAG GGAAGAGAGT TTGAGAAACA AGAAAGGCA TATGAACAAC AAAAAGACAA 6480
 ATGTGTAAAT GGAAGTAATA AGCATGATAA TGGATTTTGT GAAACACTAA CAACGTCTC 6540
 TAAAGCTAAA GACTTTTTTA AAACGTTAGG ACCATGTAAA CCTAATAATG TAGAGGGTAA 6600
 AACAATTTTT GATGATGATA AAACCTTTAA ACATACAAAA GATTGTGATC CATGTCTTAA 6660
 20 ATTTAGTGTT AATTGTAAAA AAGATGAATG TGATAATTCT AAAGGAACCG ATTGCCGAAA 6720
 TAAAAATAGT ATTGATGCAA CAGATATTGA AAATGGAGTG GATTCTACTG TACTAGAAAT 6780
 GCGTGTCACT GCTGATAGTA AAAGTGGATT TAATGGTGAT GGTTTAGAGA ATGCTTGTAG 6840
 AGGTGCTGGT ATCTTTGAAG GTATTAGAAA AGATGAATGG AAATGTCGTA ATGTATGTGG 6900
 TTATGTTGTA TGTAACCCG AAAACGTTAA TGGGGAAGCA AAGGGAAGCA ACATTATACA 6960
 25 AATTAGAGCA CTGGTTAAAC GTTGGGTAGA ATATTTTTTT GAAGATTATA ATAAATATAA 7020
 ACATAAAATT TCACATCGCA TAAAAAATGG TGAATATCT CCATGTATAA AAAATTGTGT 7080
 AGAAAAATGG GTAGATCAGA AAAGAAAAGA ATGGAAGGAA ATTACTGAAC GTTTCAAAGA 7140
 TCAATATAAA AATGACAATT CAGATGATGA CAATGTGAGA AGTTTTTTGG AGACCTTGAT 7200
 ACCTCAAATT ACTGATGCAA ACGCTAAAAA TAAGGTTATA AAATTAAGTA AGTTCGGTAA 7260
 30 TTCTGTGGA TGTAGTGCCA GTGCGAACGA ACAAACAAA AATGGTGAAT ACAAGGACGC 7320
 TATAGATTGT ATGCTTAAAA AGCTTAAAGA TAAAATTGGC GAGTGCGAAA AGAAACACCA 7380
 TCAAACTAGT GATACCGAGT GTTCCGACAC ACCACAACCG CAAACCCTTG AAGACGAAAC 7440
 TTTGGATGAT GATATAGAAA CAGAGGAGGC GAAGAAGAAC ATGATGCCGA AAATTTGTGA 7500
 AAATGTGTTA AAAACAGCAC AACAAGAGGA TGAAGGCGGT TGTGTCCCAG CAGAAAATAG 7560
 35 TGAAGAACCG GCAGCAACAG ATAGTGGTAA GGAAACCCCC GAACAAACCC CCGTTCTCAA 7620
 ACCCGAAGAA GAAGCAGTAC CGGAACACCC ACCTCCACCC CCACAGGAAA AAGCCCCGGC 7680
 ACCAATACCC CAACCACAAC CACCAACCCC CCCACACAA CTCTTGGATA ATCCCCACGT 7740
 TCTAACCGCC CTGGTGACCT CCACCCTCGC CTGGAGCGTT GGCATCGGTT TTGCTACATT 7800
 CACTTATTTT TATCTAAAGG TAAATGGAAG TATATATATG GGGATGTGGA TGTATGTGGA 7860
 40 TGTATGTGAA TGTATGTGGA TGTATGTGGA TGTATGTGGA TGTGTTTTAT GGATATGTAT 7920
 TTGTGATTAT GTTTGGATAT ATATATATAT ATATATATGT TTATGTATAT GTGTTTTTGG 7980
 ATATATATAT GTGTATGTAT ATGATTTTCT GTATATGTAT TTGTGGGTTA AGGATATATA 8040
 TATATGGATG TACTTGTATG TGTTTTATAT ATATATTTTA TATATATGTA TTTATATTAA 8100
 AAAAGAAATA TAAAAACAAA TTTATTAAAA TGAAAAAAG AAAAATGAAA TATAAAAAAA 8160
 45 AATTTATTAA AATAAAAAAA AAAAAAATA AAAAGGAGAA AAATTTTTTA AAAAATAATA 8220

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

- 50 (A) LENGTH: 2710 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

55

(iii) HYPOTHETICAL: NO

(vi) ORIGINAL SOURCE:

60

- (A) ORGANISM:
- Plasmodium falciparum*

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Asn Val Met Val Glu Leu Ala Lys Met Gly Pro Lys Glu Ala Ala Gly

BNSDOCID: <WO 9640766A2_1_>

515 520 525
 Gly Lys Leu Tyr Glu Pro Lys Pro Asp Lys Glu Gly Thr Thr Ile Thr
 530 535 540
 Ile Leu Lys Ser Gly Lys Gly His Asp Asp Ile Glu Glu Lys Leu Asn
 545 550 555 560
 Lys Phe Cys Asp Glu Lys Asn Gly Asp Thr Ile Asn Ser Gly Gly Ser
 565 570 575
 Gly Thr Gly Gly Ser Gly Gly Gly Asn Ser Gly Arg Gln Glu Leu Tyr
 580 585 590
 Glu Glu Trp Lys Cys Tyr Lys Gly Glu Asp Val Val Lys Val Gly His
 595 600 605
 Asp Glu Asp Asp Glu Glu Asp Tyr Glu Asn Val Lys Asn Ala Gly Gly
 610 615 620
 Leu Cys Ile Leu Lys Asn Gln Lys Lys Asn Lys Glu Glu Gly Gly Asn
 625 630 635 640
 Thr Ser Glu Lys Glu Pro Asp Glu Ile Gln Lys Thr Phe Asn Pro Phe
 645 650 655
 Phe Tyr Tyr Trp Val Ala His Met Leu Lys Asp Ser Ile His Trp Lys
 660 665 670
 Lys Lys Leu Gln Arg Cys Leu Gln Asn Gly Asn Arg Ile Lys Cys Gly
 675 680 685
 Asn Asn Lys Cys Asn Asn Asp Cys Glu Cys Phe Lys Arg Trp Ile Thr
 690 695 700
 Gln Lys Lys Asp Glu Trp Gly Lys Ile Val Gln His Phe Lys Thr Gln
 705 710 715 720
 Asn Ile Lys Gly Arg Gly Gly Ser Asp Asn Thr Ala Glu Leu Ile Pro
 725 730 735
 Phe Asp His Asp Tyr Val Leu Gln Tyr Asn Leu Gln Glu Glu Phe Leu
 740 745 750
 Lys Gly Asp Ser Glu Asp Ala Ser Glu Glu Lys Ser Glu Asn Ser Leu
 755 760 765
 Asp Ala Glu Glu Ala Glu Glu Leu Lys His Leu Arg Glu Ile Ile Glu
 770 775 780
 Ser Glu Asp Asn Asn Gln Glu Ala Ser Val Gly Gly Gly Val Thr Glu
 785 790 795 800
 Gln Lys Asn Ile Met Asp Lys Leu Leu Asn Tyr Glu Lys Asp Glu Ala
 805 810 815
 Asp Leu Cys Leu Glu Ile His Glu Asp Glu Glu Glu Lys Glu Lys
 820 825 830
 Gly Asp Gly Asn Glu Cys Ile Glu Glu Gly Glu Asn Phe Arg Tyr Asn
 835 840 845
 Pro Cys Ser Gly Glu Ser Gly Asn Lys Arg Tyr Pro Val Leu Ala Asn
 850 855 860
 Lys Val Ala Tyr Gln Met His His Lys Ala Lys Thr Gln Leu Ala Ser
 865 870 875 880
 Arg Ala Gly Arg Ser Ala Leu Arg Gly Asp Ile Ser Leu Ala Gln Phe
 885 890 895
 Lys Asn Gly Arg Asn Gly Ser Thr Leu Lys Gly Gln Ile Cys Lys Ile
 900 905 910
 Asn Glu Asn Tyr Ser Asn Asp Ser Arg Gly Asn Ser Gly Gly Pro Cys
 915 920 925
 Thr Gly Lys Asp Gly Asp His Gly Gly Val Arg Met Arg Ile Gly Thr
 930 935 940
 Glu Trp Ser Asn Ile Glu Gly Lys Lys Gln Thr Ser Tyr Lys Asn Val
 945 950 955 960
 Phe Leu Pro Pro Arg Arg Glu His Met Cys Thr Ser Asn Leu Glu Asn
 965 970 975
 Leu Asp Val Gly Ser Val Thr Lys Asn Asp Lys Ala Ser His Ser Leu
 980 985 990
 Leu Gly Asp Val Gln Leu Ala Ala Lys Thr Asp Ala Ala Glu Ile Ile
 995 1000 1005
 Lys Arg Tyr Lys Asp Gln Asn Asn Ile Gln Leu Thr Asp Pro Ile Gln
 1010 1015 1020

Gln Lys Asp Gln Glu Ala Met Cys Arg Ala Val Arg Tyr Ser Phe Ala
 1025 1030 1035 1040
 Asp Leu Gly Asp Ile Ile Arg Gly Arg Asp Met Trp Asp Glu Asp Lys
 1045 1050 1055
 5 Ser Ser Thr Asp Met Glu Thr Arg Leu Ile Thr Val Phe Lys Asn Ile
 1060 1065 1070
 Lys Glu Lys His Asp Gly Ile Lys Asp Asn Pro Lys Tyr Thr Gly Asp
 1075 1080 1085
 10 Glu Ser Lys Lys Pro Ala Tyr Lys Lys Leu Arg Ala Asp Trp Trp Glu
 1090 1095 1100
 Ala Asn Arg His Gln Val Trp Arg Ala Met Lys Cys Ala Thr Lys Gly
 1105 1110 1115 1120
 Ile Ile Cys Pro Gly Met Pro Val Asp Asp Tyr Ile Pro Gln Arg Leu
 1125 1130 1135
 15 Arg Trp Met Thr Glu Trp Ala Glu Trp Tyr Cys Lys Ala Gln Ser Gln
 1140 1145 1150
 Glu Tyr Asp Lys Leu Lys Lys Ile Cys Ala Asp Cys Met Ser Lys Gly
 1155 1160 1165
 20 Asp Gly Lys Cys Thr Gln Gly Asp Val Asp Cys Gly Lys Cys Lys Ala
 1170 1175 1180
 Ala Cys Asp Lys Tyr Lys Glu Glu Ile Glu Lys Trp Asn Glu Gln Trp
 1185 1190 1195 1200
 Arg Lys Ile Ser Asp Lys Tyr Asn Leu Leu Tyr Leu Gln Ala Lys Thr
 1205 1210 1215
 25 Thr Ser Thr Asn Pro Gly Arg Thr Val Leu Gly Asp Asp Asp Pro Asp
 1220 1225 1230
 Tyr Gln Gln Met Val Asp Phe Leu Thr Pro Ile His Lys Ala Ser Ile
 1235 1240 1245
 30 Ala Ala Arg Val Leu Val Lys Arg Ala Ala Gly Ser Pro Thr Glu Ile
 1250 1255 1260
 Ala Ala Ala Ala Pro Ile Thr Pro Tyr Ser Thr Ala Ala Gly Tyr Ile
 1265 1270 1275 1280
 His Gln Glu Ile Gly Tyr Gly Gly Cys Gln Glu Gln Thr Gln Phe Cys
 1285 1290 1295
 35 Glu Lys Lys His Gly Ala Thr Ser Thr Ser Thr Thr Lys Glu Asn Lys
 1300 1305 1310
 Glu Tyr Thr Phe Lys Gln Pro Pro Glu Tyr Ala Thr Ala Cys Asp
 1315 1320 1325
 40 Cys Ile Asn Arg Ser Gln Thr Glu Glu Pro Lys Lys Lys Glu Glu Asn
 1330 1335 1340
 Val Glu Ser Ala Cys Lys Ile Val Glu Lys Ile Leu Glu Gly Lys Asn
 1345 1350 1355 1360
 Gly Arg Thr Thr Val Gly Glu Cys Asn Pro Lys Glu Ser Tyr Pro Asp
 1365 1370 1375
 45 Trp Asp Cys Lys Asn Asn Ile Asp Ile Ser His Asp Gly Ala Cys Met
 1380 1385 1390
 Pro Pro Arg Arg Gln Lys Leu Cys Leu Tyr Tyr Ile Ala His Glu Ser
 1395 1400 1405
 50 Gln Thr Glu Asn Ile Lys Thr Asp Asp Asn Leu Lys Asp Ala Phe Ile
 1410 1415 1420
 Lys Thr Ala Ala Ala Glu Thr Phe Leu Ser Trp Gln Tyr Tyr Lys Ser
 1425 1430 1435 1440
 Lys Asn Asp Ser Glu Ala Lys Ile Leu Asp Arg Gly Leu Ile Pro Ser
 1445 1450 1455
 55 Gln Phe Leu Arg Ser Met Met Tyr Thr Phe Gly Asp Tyr Arg Asp Ile
 1460 1465 1470
 Cys Leu Asn Thr Asp Ile Ser Lys Lys Gln Asn Asp Val Ala Lys Ala
 1475 1480 1485
 60 Lys Asp Lys Ile Gly Lys Phe Phe Ser Lys Asp Gly Ser Lys Ser Pro
 1490 1495 1500
 Ser Gly Leu Ser Arg Gln Glu Trp Trp Lys Thr Asn Gly Pro Glu Ile
 1505 1510 1515 1520
 Trp Lys Gly Met Leu Cys Ala Leu Thr Lys Tyr Val Thr Asp Thr Asp
 1525 1530 1535

Asn Lys Arg Lys Ile Lys Asn Asp Tyr Ser Tyr Asp Lys Val Asn Gln
 1540 1545 1550
 Ser Gln Asn Gly Asn Pro Ser Leu Glu Glu Phe Ala Ala Lys Pro Gln
 1555 1560 1565
 Phe Leu Arg Trp Met Ile Glu Trp Gly Glu Glu Phe Cys Ala Glu Arg
 1570 1575 1580
 Gln Lys Lys Glu Asn Ile Ile Lys Asp Ala Cys Asn Glu Ile Asn Ser
 1585 1590 1595 1600
 Thr Gln Gln Cys Asn Asp Ala Lys His Arg Cys Asn Gln Ala Cys Arg
 1605 1610 1615
 Ala Tyr Gln Glu Tyr Val Glu Asn Lys Lys Lys Glu Phe Ser Gly Gln
 1620 1625 1630
 Thr Asn Asn Phe Val Leu Lys Ala Asn Val Gln Pro Gln Asp Pro Glu
 1635 1640 1645
 Tyr Lys Gly Tyr Glu Tyr Lys Asp Gly Val Gln Pro Ile Gln Gly Asn
 1650 1655 1660
 Glu Tyr Leu Leu Gln Lys Cys Asp Asn Asn Lys Cys Ser Cys Met Asp
 1665 1670 1675 1680
 Gly Asn Val Leu Ser Val Ser Pro Lys Glu Lys Pro Phe Gly Lys Tyr
 1685 1690 1695
 Ala His Lys Tyr Pro Glu Lys Cys Asp Cys Tyr Gln Gly Lys His Val
 1700 1705 1710
 Pro Ser Ile Pro Pro Pro Pro Pro Val Gln Pro Gln Pro Glu Ala
 1715 1720 1725
 Pro Thr Val Thr Val Asp Val Cys Ser Ile Val Lys Thr Leu Phe Lys
 1730 1735 1740
 Asp Thr Asn Asn Phe Ser Asp Ala Cys Gly Leu Lys Tyr Gly Lys Thr
 1745 1750 1755 1760
 Ala Pro Ser Ser Trp Lys Cys Ile Pro Ser Asp Thr Lys Ser Gly Ala
 1765 1770 1775
 Gly Ala Thr Thr Gly Lys Ser Gly Ser Asp Ser Gly Ser Ile Cys Ile
 1780 1785 1790
 Pro Pro Arg Arg Arg Arg Leu Tyr Val Gly Lys Leu Gln Glu Trp Ala
 1795 1800 1805
 Thr Ala Leu Pro Gln Gly Glu Gly Ala Ala Pro Ser His Ser Arg Ala
 1810 1815 1820
 Asp Asp Leu Arg Asn Ala Phe Ile Gln Ser Ala Ala Ile Glu Thr Phe
 1825 1830 1835 1840
 Phe Leu Trp Asp Arg Tyr Lys Glu Glu Lys Lys Pro Gln Gly Asp Gly
 1845 1850 1855
 Ser Gln Gln Ala Leu Ser Gln Leu Thr Ser Thr Tyr Ser Asp Asp Glu
 1860 1865 1870
 Glu Asp Pro Pro Asp Lys Leu Leu Gln Asn Gly Lys Ile Pro Pro Asp
 1875 1880 1885
 Phe Leu Arg Leu Met Phe Tyr Thr Leu Gly Asp Tyr Arg Asp Ile Leu
 1890 1895 1900
 Val His Gly Gly Asn Thr Ser Asp Ser Gly Asn Thr Asn Gly Ser Asn
 1905 1910 1915 1920
 Asn Asn Asn Ile Val Leu Glu Ala Ser Gly Asn Lys Glu Asp Met Gln
 1925 1930 1935
 Lys Ile Gln Glu Lys Ile Glu Gln Ile Leu Pro Lys Asn Gly Gly Thr
 1940 1945 1950
 Pro Leu Val Pro Lys Ser Ser Ala Gln Thr Pro Asp Lys Trp Trp Asn
 1955 1960 1965
 Glu His Ala Glu Ser Ile Trp Lys Gly Met Ile Cys Ala Leu Thr Tyr
 1970 1975 1980
 Thr Glu Lys Asn Pro Asp Thr Ser Ala Arg Gly Asp Glu Asn Lys Ile
 1985 1990 1995 2000
 Glu Lys Asp Asp Glu Val Tyr Glu Lys Phe Phe Gly Ser Thr Ala Asp
 2005 2010 2015
 Lys His Gly Thr Ala Ser Thr Pro Thr Gly Thr Tyr Lys Thr Gln Tyr
 2020 2025 2030
 Asp Tyr Glu Lys Val Lys Leu Glu Asp Thr Ser Gly Ala Lys Thr Pro
 2035 2040 2045

Ser Ala Ser Ser Asp Thr Pro Leu Leu Ser Asp Phe Val Leu Arg Pro
 2050 2055 2060
 Pro Tyr Phe Arg Tyr Leu Glu Glu Trp Gly Gln Asn Phe Cys Lys Lys
 2065 2070 2075 2080
 5 Arg Lys His Lys Leu Ala Gln Ile Lys His Glu Cys Lys Val Glu Glu
 2085 2090 2095
 Asn Gly Gly Gly Ser Arg Arg Gly Gly Ile Thr Arg Gln Tyr Ser Gly
 2100 2105 2110
 Asp Gly Glu Ala Cys Asn Glu Met Leu Pro Lys Asn Asp Gly Thr Val
 2115 2120 2125
 10 Pro Asp Leu Glu Lys Pro Ser Cys Ala Lys Pro Cys Ser Ser Tyr Arg
 2130 2135 2140
 Lys Trp Ile Glu Ser Lys Gly Lys Glu Phe Glu Lys Gln Glu Lys Ala
 2145 2150 2155 2160
 15 Tyr Glu Gln Gln Lys Asp Lys Cys Val Asn Gly Ser Asn Lys His Asp
 2165 2170 2175
 Asn Gly Phe Cys Glu Thr Leu Thr Thr Ser Ser Lys Ala Lys Asp Phe
 2180 2185 2190
 Leu Lys Thr Leu Gly Pro Cys Lys Pro Asn Asn Val Glu Gly Lys Thr
 2195 2200 2205
 20 Ile Phe Asp Asp Asp Lys Thr Phe Lys His Thr Lys Asp Cys Asp Pro
 2210 2215 2220
 Cys Leu Lys Phe Ser Val Asn Cys Lys Lys Asp Glu Cys Asp Asn Ser
 2225 2230 2235 2240
 25 Lys Gly Thr Asp Cys Arg Asn Lys Asn Ser Ile Asp Ala Thr Asp Ile
 2245 2250 2255
 Glu Asn Gly Val Asp Ser Thr Val Leu Glu Met Arg Val Ser Ala Asp
 2260 2265 2270
 Ser Lys Ser Gly Phe Asn Gly Asp Gly Leu Glu Asn Ala Cys Arg Gly
 2275 2280 2285
 30 Ala Gly Ile Phe Glu Gly Ile Arg Lys Asp Glu Trp Lys Cys Arg Asn
 2290 2295 2300
 Val Cys Gly Tyr Val Val Cys Lys Pro Glu Asn Val Asn Gly Glu Ala
 2305 2310 2315 2320
 35 Lys Gly Lys His Ile Ile Gln Ile Arg Ala Leu Val Lys Arg Trp Val
 2325 2330 2335
 Glu Tyr Phe Phe Glu Asp Tyr Asn Lys Ile Lys His Lys Ile Ser His
 2340 2345 2350
 Arg Ile Lys Asn Gly Glu Ile Ser Pro Cys Ile Lys Asn Cys Val Glu
 2355 2360 2365
 40 Lys Trp Val Asp Gln Lys Arg Lys Glu Trp Lys Glu Ile Thr Glu Arg
 2370 2375 2380
 Phe Lys Asp Gln Tyr Lys Asn Asp Asn Ser Asp Asp Asp Asn Val Arg
 2385 2390 2395 2400
 45 Ser Phe Leu Glu Thr Leu Ile Pro Gln Ile Thr Asp Ala Asn Ala Lys
 2405 2410 2415
 Asn Lys Val Ile Lys Leu Ser Lys Phe Gly Asn Ser Cys Gly Cys Ser
 2420 2425 2430
 Ala Ser Ala Asn Glu Gln Asn Lys Asn Gly Glu Tyr Lys Asp Ala Ile
 2435 2440 2445
 50 Asp Cys Met Leu Lys Lys Leu Lys Asp Lys Ile Gly Glu Cys Glu Lys
 2450 2455 2460
 Lys His His Gln Thr Ser Asp Thr Glu Cys Ser Asp Thr Pro Gln Pro
 2465 2470 2475 2480
 55 Gln Thr Leu Glu Asp Glu Thr Leu Asp Asp Asp Ile Glu Thr Glu Glu
 2485 2490 2495
 Ala Lys Lys Asn Met Met Pro Lys Ile Cys Glu Asn Val Leu Lys Thr
 2500 2505 2510
 Ala Gln Gln Glu Asp Glu Gly Gly Cys Val Pro Ala Glu Asn Ser Glu
 2515 2520 2525
 60 Glu Pro Ala Ala Thr Asp Ser Gly Lys Glu Thr Pro Glu Gln Thr Pro
 2530 2535 2540
 Val Leu Lys Pro Glu Glu Ala Val Pro Glu Pro Pro Pro Pro Pro
 2545 2550 2555 2560

Pro Gln Glu Lys Ala Pro Ala Pro Ile Pro Gln Pro Gln Pro Pro Thr
 2565 2570 2575
 Pro Pro Thr Gln Leu Leu Asp Asn Pro His Val Leu Thr Ala Leu Val
 2580 2585 2590
 5 Thr Ser Thr Leu Ala Trp Ser Val Gly Ile Gly Phe Ala Thr Phe Thr
 2595 2600 2605
 Tyr Phe Tyr Leu Lys Val Asn Gly Ser Ile Tyr Met Gly Met Trp Met
 2610 2615 2620
 10 Tyr Val Asp Val Cys Glu Cys Met Trp Met Tyr Val Asp Val Cys Gly
 2625 2630 2635 2640
 Cys Val Leu Trp Ile Cys Ile Cys Asp Tyr Val Trp Ile Tyr Ile Tyr
 2645 2650 2655
 Ile Tyr Ile Cys Leu Cys Ile Cys Val Phe Gly Tyr Ile Tyr Val Tyr
 2660 2665 2670
 15 Val Tyr Asp Phe Leu Tyr Met Tyr Leu Trp Val Lys Asp Ile Tyr Ile
 2675 2680 2685
 Trp Met Tyr Leu Tyr Val Phe Tyr Ile Tyr Ile Leu Tyr Ile Cys Ile
 2690 2695 2700
 20 Tyr Ile Lys Lys Glu Ile
 2705 2710

(2) INFORMATION FOR SEQ ID NO:13:

- 25 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 19124 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

- 30 (ii) MOLECULE TYPE: cDNA
 (iii) HYPOTHETICAL: NO
 (iv) ANTI-SENSE: NO

- 35 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

ACATTTTTC GTAATATATA TATATATATA TATATATAAT TCTCTTTTC TAATATATAT
 60
 ATCCTTCTAT TTTCGATTTT TTCATTTTTC TCCAGTATTA ATTTATTTAT TTATTTGTGA 120
 TATTTTATAA TATATTATTT AAATGTGTAT TTATATATGT GTTTTATTTT TGTTATTAAT 180
 40 TTGAATAATC CGAGCGAAAA AAAATATATA ATCTCATATA AAAATTATTT ATAATACAAT 240
 ATTATATAGT TTCCTATTAA AATAAATTAA TATAATATAC AATAATATTT CTGTGTTATTT 300
 TTATAAATAT AACTAATTTT TTATTTTAT TTAACTTTAT TCCTTTTAA TTTCTTAATT 360
 CTTTTATGCA AACAAAAAAC ATAAAGTAAT TCTACATATC AACAAAAAAA AAAAAAAA 420
 45 AAAAAAAA ATTTATTATA ATATAATAA AAATATAAAG ACATACGTTT ACTTATTATT 480
 ATAAATGATT TATTACGATT AAAACATATT GAGATTATAA TAATATAATT TAACATAGAA 540
 AGAGTTAAGA ATACATTTT TTTTTTTTTT TGATATGTAA TTCAACATAT ATATATATAT 600
 ATATCTTTT AATTTAATTA AATAAAATTC CTTATTATTC ATATTGTTTC TTTATCACA 660
 TGTGAAATAT TAAAAATAAT TTTCGATTTT ATCGATATAT TTATGTCGTT TATATACTTA 720
 TATAGGTCTT TATAACTATT GATTAATAGA AGGTAATAGC CTAATAATAT AAATACTCGT 780
 50 ATTTATAAAT TCATTTATAT ATTTCAAATA TATTTTCGATG GTTTATTTTC AAATACAATT 840
 AATTAGATTT CTAAATATT TCTTCATTTA TTCATTTTAA TAGCATATAC ATGCACATTA 900
 TAAATTATTA ATAAAAAATT TTTATTTTAA TATATAATAA CAATTTTCAT ACATTACATT 960
 TTTCACACAA CATTTAAGTT GTCATAATGT AACACATTAA ATAATATATT ACTTATATAT 1020
 ATATAATTAT TAATTATATA TTAAATAAAA ATGTATTATC GCCTGTATTA TCATAGTATA 1080
 55 TATAATGTTG TATAACGCTT CAAAATATAT ATAATAATAT AATTAAAAAT ATATATATAG 1140
 TAATTAATTA TTTTGTTATG TTATGTAATA ATGCAATTAA TATAAGATAA AATTCTATAG 1200
 CTATTATTTA AAATATATAT ATATATATAT ATATTAGTAT ATGTTATCAA 1260
 AATATTATAA TATGTAAATT ATTAATAAAA TATATTTGTA TAACATACAA GACTAAAGAA 1320
 AACTATACAA TCTGGTATCT AATAGTATAT ATATATAATA TCTTTTTTAT TTAATTGTTT 1380
 60 TCTCTTTTTT TTTTTTTTAA ATAATAATAA ATATTAATAT ATTTTTTTTC ATAATTATAT 1440
 GATTTAGTAT TTTAATAATA AATAAATCTT TTAATAAACT TCAAAACATT TTTGCATAAA 1500
 ATAATATTA TATTAGTAAC CACCTAGATA AATTAGAGAG AAACGTAGAA CATACCAAAA 1560
 AAAATTAGAA CAAAAAGAAT ATTACAAAA ATAATAAAT TAAATTATTT CTTTACTATT 1620
 AATTTAAGT TTTTTTTCAT ATCATATATT ATGATACACA ATGTTTGTTT TTAATGTTT 1680

	TATATACATG	CAATGATATG	TTTCTGTTGG	AATATGTATT	ATATACTTAT	ATGTTCTAAT	1740
	AAATGTATTG	TACACCTTTA	GCAACTATTA	CTACACACAT	TTTTATATAA	TTTATAACAG	1800
	GAAATATAGT	TATATTATTA	CAATATCTTA	ATGTGTTTTT	GCAAAAATAT	AAAAACAAG	1860
	AAAATTACAA	TTGTAATTAA	TCGTATGACA	TAAAATTATA	TTATATTAGA	AATTAAAAAT	1920
5	CAAAATTATA	AAAAATATGG	AAATGTTTTG	TTATATTATT	TTTTTAAAAA	TTTAATTATT	1980
	TTATTTTTATT	ATTTATTTTT	TTTTTTTTTT	GTGTTCTAAA	TAAAAAGGCA	AATATGATTC	2040
	AAGTAAAAAA	TATATATATT	TACATAATGG	CAAAATAATT	GTTTATTATA	TTATATGACT	2100
	ATAATAATAT	TTTAGATTAA	ACATATGTAA	TTCATTTAAC	AGAATAAAAA	AAAATATTAT	2160
	ATATATATAT	TAATTATTAA	GTTATAGATT	TAATAAAAAA	ATATTATACA	TATGAGATTA	2220
10	AAAATGAAAG	TTCACCTACAG	TAATATATTA	TTATATGTCG	TCAATTTAAG	TATATTCTTA	2280
	ATATCACGTA	TGCACTAAAT	AATGACAATA	ATAATATATA	TGTAACATTT	TATAATTGAT	2340
	GTAAATAAAA	AAATATACAT	ATATACAAAA	ACATATATGA	TATTTACATT	CTTTTTTATA	2400
	GATAAATATC	CAGAAGAAGT	ATTACATCAC	TTCACCTCAT	ATACCAAACA	CGAAAAAAAT	2460
	ACAACCACTA	GGTTATTATG	CGAATGTGAC	TTATATACGT	CCATTTTATGA	TAATGACCCG	2520
15	GAAATGATAT	TAGTGATGGA	AAATTTCAAT	AAACAGACAG	AAGAAAGGTT	TCATGAATAC	2580
	AATGAACGCA	TGCAAGAAAA	ACGAAAAATA	TGTAAAGAAC	AATGCGAAAA	GGATATACAA	2640
	AAAATTATTT	TAAAAGATAA	AATCGAAAAA	GAATTAACAG	AAAAGTTAGA	GGCATTTGGA	2700
	ACGAATATAA	AGACTGAGGA	TATACCTACT	TGTGTATGCG	AAAAATCAGT	AGCAGATATA	2760
	GTGGAAAAAA	CGTGTTTGAA	ATGTGGAGGT	ATATTGGGTG	TTGGTGTGAC	TCCATCTTTA	2820
20	GGTTTATTAG	GAGAAATAGG	TGGACTTGTT	ATAAATAATT	GGACAAATAC	TCCTTTTTTAT	2880
	AAAGCTTTTC	TTACTTTTGC	TCAAAAGGAA	GGTATAGCTG	CCGGTAAAAA	TGCTAGTGAT	2940
	ACTGCTCGTA	TTGATACAGT	TATTTAAGGA	ATAATATCAA	ATTTTGATGT	GCACACTATA	3000
	AATGGTTCTA	CGTTGGGGAA	AGTTATTACC	GTAGAAGCTC	TTAAGGATGA	CACTACTCTT	3060
	ACTACGGCAC	TATATAATGA	ATATGTAAGC	ATGTGTGTAA	ATACGAACCC	TGTCGAAGAC	3120
25	AAATTAATTT	GTGCTTTTGG	GATGAGAGAC	GGTCTAGTTG	CAGGGCAATA	TGCTTCATCG	3180
	CGAGACGTTA	TAGGATCAAG	TGTAAAAGGA	ATTATTAGAA	AAGCTGCAAA	CGCTGCTTCA	3240
	CAAGCTGCTG	AGACAGCTGC	TAACGAAACT	ACTTCCGGAA	TGATCGAAGC	CGAGTTAAGT	3300
	AAAATAACAT	CTGCAGGTGC	TAATTTACAC	AGTGCAATTA	CTTACTCAGT	AACTGCGATA	3360
	TTGGTTATAG	TTTTGGTTAT	GGTAATTATT	TATTTAATAT	TACGTTATCG	TAGAAAAAAA	3420
30	AAAATGAAGA	AAAAATTGCA	ATATATAAAA	TTATTAAGG	AATAGATATA	CGATGTCGAG	3480
	CTATTAGCGG	TAAATTAAAG	TATTTGTAAAT	TTTTTCATTA	ATATGCTATG	ATCATTTGAT	3540
	AATTAATTTT	TTTTTATAAT	ATTATATTTT	TTTATACCTT	GGATTCTTAC	ATTGTTTTTAT	3600
	TATTATATGA	TTATTTAATT	ATTATACTTA	TATATATATA	TATTTTTTACA	TTAAGATATT	3660
	ATATATGTAT	CTATCTATCT	ATCTATCTAT	ATATATATAT	ATATATATAT	ATTATAATAA	3720
35	TTATTATTAT	TAGATGCATA	TTAGTGATGA	TTATAATAAT	AACCTATTGA	AGAGAATAGA	3780
	ACATAATAAT	ATATTAAATT	AATAGAAGTT	CATTTTATT	GTTATATGTA	TATAAAAAATA	3840
	AGAAATTTGA	AAAAGTAATT	TACACATGAT	AATGTATTTT	ATTTTATTTG	TGTTGTTTTA	3900
	TATTTATTTA	TAAAAATTGT	TTAATATAAG	TTGTTTATAT	AATTTTTTAA	TATGGCACCA	3960
	TTAGCTTTCC	ATTATACAAA	TATATATTTT	CTCATTAGAA	TCTGAATATT	TATTGTATTA	4020
40	TAAAAAAAGT	ATAATATAAT	AAAATATCTA	AGATTTTTTC	TAATTTGTTT	AATTTATAAT	4080
	AAATTTTAAT	TTTATACGAT	AGAATAAATT	ATAATCAACA	TATATATATG	TATTCATCTT	4140
	AAGAACCCTAG	TACAATATAG	TAACAACCTG	TTCTTTTTTA	TTATAAATAA	CATAAGAATG	4200
	TGTAAAAGGA	TAGTTGTTAA	AGGCTTTTTT	AATATTGATT	ATAAATGTTT	GTAAGATATA	4260
	TGATAATAGAT	ATCTTAACAT	ACAACCTTGC	ATAAATGTTA	TAAAAAATAA	ATATATAATA	4320
45	AGAAATATTA	TAAATAATAT	TATAAAAAAT	TAAGCATAAA	TGTCACAATA	AATTTTTTTT	4380
	TATTAATTTA	ATTTTATTTT	ATTGTTCTAA	AATATATTGA	TTATGAGAAT	ATTATTTGTG	4440
	TCTAATATAA	TTAAGATATT	TCTAATATTA	ATTTATATAT	ATATATTTAA	AAGTATTTTA	4500
	AGAATAATTT	TTTACTTATT	TATTATAATA	TGAAATATGC	ATGGAGTATA	TATAAATATT	4560
	GATGACAAAA	AAAAAACTTT	TAAAATGGAA	AATATGCATA	TAATAAAATA	CTATATAGTA	4620
50	TAATTTGGTA	AATAGTTGTA	ACTTATACAA	ACATGTTGCA	TTCATAATTT	AGAGATTATG	4680
	TAATATTGTT	TATGTATCGT	AATATATATT	AATATAATTG	TTTTTTTAGT	ATGTATGGTA	4740
	TTCTAATAAT	ATATTCATAT	GTAGTCATAG	TGTCAATGAA	TATAAAATAT	GGTATATTTA	4800
	TATTATTGTA	TATATTAAAT	AAGTAACACA	GAACATTATA	TATAGTAATA	AATAGAAGAA	4860
	ATAATATATT	TTTATGTTAT	ATATTATTAG	TTATTATAAA	GGGGAAAATT	CATAATATTT	4920
55	ATGAAAATTT	TTGTATATGA	TATAGTTATA	AGTTAAAAAA	AAAAAAAAC	AAGAACAAAA	4980
	ATGGAAAGCA	TAAAAAATGT	TACTGTAATA	GGATAAAAAA	TATTATATAA	AATGTTTATT	5040
	TTATCTTAAA	AAGGTTCTTA	TTATAACATT	AAAAAAAATT	TGTCCTCATTT	TATAAATAAT	5100
	TAACTACATT	TACATAATGA	AAATTCGATT	TTGTGTTTTT	TTGATGAATA	TGATGAATA	5160
	ATTATTTTATA	TGTGAATGCG	TTCTATATAA	TAATAATAAT	TTTATTTTAA	AAAATGAAAA	5220
60	ATAAGAAATA	AATATCCTGA	TTTTGTAGTT	CCAATAGCTT	AATATAATTA	TGGACTCATA	5280
	TATATATTAT	ATATATCTTT	ACAACAAGTA	ATAAGTAAAT	ATTATTTTAA	TCTTAATAAG	5340
	GAAAAATAAA	ATAATAAAAT	AAGAATACTG	AATAATAAGT	CATATTATAC	ATTTTTTAAA	5400
	AATGTAACAT	AATTACAAAT	ACGTAACATG	TATTATAGAA	ATAATAAGAA	TTTAATATTA	5460
	AGGATAAATA	TAAATATTTA	AAATTATATT	TTTTTATGTC	AATTTATGTT	ATATTATATT	5520

ATATTAACAT GATTAGTTTT TTGAAAAATA TTTAAATATC ATATAATAAT AATAAATTAG 5580
TTAAAAATAAT AGTATTTTCAT ACAAATACT AACTTATAAG TATATCATAT AATATTATAT 5640
ATATATATAT TTATGTGTTT TTGATTGGGT GTATATAAGG CTATAAGTAT ATATGGGTG 5700
5 TTCATTATAT ATTTATATGT GAATAGATAC ATATAAGTTA ATATATTTTAT TTGTGTATAT 5760
GTCTGTGTTA AGATAGATAT GCATTACAGT TAAGGGTTAT AGTTTTTTTTT TTTTTTTTTT 5820
GTACATATAT ATAAAAATA GATAACTAAC AATATGCATA TTACAAGAAT AATATTTGTA 5880
TAAATATAT ATATATATAT ATATATAAAG ACATTAAAAC TATACTAATA GGTAAATTAGT 5940
TTTATTATAT CATCCTTTTA TTATTATAAT TTTTTTTGTT TTACTTCTTG TCGTTCTTTT 6000
10 TTGTTATTAT AATATAACAA ATATAAAACA ATATCAGTAT TTGGAATATA AATAAATTTA 6060
TTCTACATAT ATGCATATAT ATATATATAT ATATATATAT ATATATATAT ATATATATAT 6120
ATATGTATGA TTTTATACTA TTTTATACA TGCATTTTTA TATATTTTAG TATATACTTT 6180
AAAGATATTA TTAATATTTA TATAGTAGCA TATATGTATT TATATTATAA CAAATATTTT 6240
CATTTATATA AATATATAGA ACATGAACAT TTTATTAATA ACTCATATT GAATATATAT 6300
15 ATTTATAATG TGTATTTTTT CTTATTTTTT TATATTATAC AATAAAATTT TGAAATTCAT 6360
AAAATGCATG AAATACATAA AAAAATACAA CAAAACAAAT GATAAAAAACA TTTTATTAA 6420
TATAATATAA TATAATATAA TAATATATTT TTCTGTAT TTATTTATCA TTTTTTTTTT 6480
GATGCTATAT ATATTATTAT ATAATAAATT ATAATATATA ACAACAAAAA TTAATAATAA 6540
TAATATACTA CTTTAAATAT AATACAACA TACAAAGAAT ATGTATCTAT ATCAATTATA 6600
20 TATATATGAA TATATAAATA TGATAGATAA TATAGATAGA GAGAAACGAA GAACATATTT 6660
GTCTCTTTTG TTATCTCTAA TATATATATA TATATAATAA ATTAAAAATA AGTCAAAAA 6720
AATATACATA TATTAATGTT AATAATTAAA TATATAAACA CGTTGCATAT ATACTTTTTT 6780
ATATGTTTGT ATTTTCGTAT TTTTTTTTTT TCATTTATAA TTTTACTTAA TAAATAAAAC 6840
ATAAAAAAAA TAATATATAT ATAATTAAT AGATAAATAA AGGAATACAT AAAATATAAT 6900
25 ATTTCTGATT ATATTTTTT TTTGTTAGAA TATTTAAAT TATTATAAAT TTATTAATAT 6960
ATATATATAT TTTTTTTAAA AATATATAA ACTAATAAT ATTATTATAT ACATATTTAA 7020
TATTATTTTT TTAACATATA CATATATTGT AATATTATAA TAGTACAAT ATTAATATAT 7080
ATATATATAT ATATACAATA TTTATATATA TTGTAATACA TAAATTATAC CTTACATATA 7140
TATATACATT CACAAAAGTG TTATATTCT TATTCTACCA TATTATAATA CTACTGTAAT 7200
ATACATATAT ACATACCCCC ACGTACGTAC GAAACACCAC CAAACCATGT ATCACGTATG 7260
30 TATGTATGCC ACGATATAAA CCACGTACCA CGTATGACAT AATGTAATGG TGGAGTTAGC 7320
AAAAATGGGG CCAAGGAGG CTGCAGGTGG GGTATGATT GAGGATGAAA GTGCCAAACA 7380
TATGTTTGAT AGGATAGGAA AAGATGTGTA CGATAAAGTA AAAGAGGAAG CTAAGAAACG 7440
TGGTAAAGGC TTGCAAGGAC GTTGTGTCAGA AGCAAAATTT GAGAAAAATG AAAGCGATCC 7500
35 ACAAACACCA GAAGATCCAT GCGATCTTGA TCATAAATAT CATACAAATG TAACTACTAA 7560
TGTAATTAAAT CCGTGCGCTG ATAGATCTGA CGTGCGTTTT TCCGATGAAT ATGGAGGTCA 7620
ATGTACACAT AATAGAATAA AAGATAGTCA ACAGGGTGAT AATAAAGGTG CATGTGCTCC 7680
ATATAGGCGA TTGCATGTAT GCGATCAAAA TTTAGAACAG ATAGAGCCTA TAAAAATAAC 7740
AAATACTCAT AATTTATTGG TAGATGTGTG TATGGCAGCA AAATTTGAAG GACAATCAAT 7800
40 AACACAAGAT TATCCAAAAT ATCAAGCAAC ATATGGTGAT TCTCCTTCTC AAATATGTAC 7860
TATGCTGGCA CGAAGTTTTG CGGACATAGG GGACATTGTC AGAGGAAGAG ATTTGTATTT 7920
AGGTAATCCA CAAGAAATAA AACAAAGACA ACAATTAGAA AATAATTTGA AAACAATTTT 7980
CGGGAATAA TATGAAAAAT TGAATGGCGC AGAAGCAGC TACGGAAATG ATCCGGAATT 8040
TTTTAAATTA CGAGAAGATT GTTGGACTGC TAATCGAGAA ACAGTATGGA AAGCCATCAC 8100
45 ATGTAACGCT TGGGGTAATA CATATTTTCA TGCAACGTGC AATAGAGGAG AACGAACTAA 8160
AGGTACTGCG CCGTGTAACG ACGACCAAGT TCCCACATAT TTTGATTATG TGCCGCAGTA 8220
TCTTCGCTGG TTCGAGGAAT GGGCAGAAGA TTTTGTAGG AAAAAAATA AAAAAATAA 8280
AGATGTTAAA AGAAATTGTC GTGGAAAAGA TAAAGAGGAT AAGGATCGAT ATTGTAGCCG 8340
TAATGGCTAC GATTGCGAAA AAACATAACG AGCGATTGGT AAGTTGCGTT ATGGTAAGCA 8400
50 ATGCATTAGC TGTTTGTATG CATGTAATCC TTACGTTGAT TGGATAAATA ACCAAAAAGA 8460
ACAATTTGAC AAACAGAAAA AAAAATATGA TGAAGAAATA AAAAAATATG AAAATGGAGC 8520
ATCAGGTGGT AGTAGGCAAA AACGGGATGC AGGTGGTACA ACTACTACTA ATTATGATGG 8580
ATATGAAAAA AAATTTTATG ACGAECTTAA TAAAAGTGAA TATAGAACCG TTGATAAAT 8640
TTTGAAAAA TTAAGTAATG AAGAAATATG CACAAAAGTT AAAGACGAAG AAGGAGGAAC 8700
55 AATTGATTTT AAAAACGTTA ATAGTGATAG TACTAGTGGT GCTAGTGGCA CTAATGTTGA 8760
AAGTCAAGGA ACATTTTATC GTTCAAATA TTGCCAACCC TGCCCTTATT GTGGAGTGAA 8820
AAAGGTAAT AATGGTGGTA GTAGTAATGA ATGGGAAGAG AAAAAAATG GCAAGTGCAA 8880
GAGTGAAAA CTTTATGAGC CTAAACCCGA CAAAGAAGGT ACTACTATTA CAATCCTTAA 8940
AAGTGGTAAA GGACATGATG ATATTGAAGA AAAATTAAAC AAATTTTGTG ATGAAAAA 9000
60 TGGTGATACA ATAAATAGTG GTGGTAGTGG TACGGGTGGT AGTGGTGGTG GTAACAGTGG 9060
TAGACAGGAA TTGTATGAAG AATGGAAATG TTATAAAGGT GAAGATGTAG TGAAAGTTGG 9120
ACACGATGAG GATGACGAGG AGGATTATGA AAATGTAAAA AATGCAGGCG GATTATGTAT 9180
ATTAAAAAAC CAAAAAAGA ATAAAGAAGA AGGTGGAAT ACGTCTGAAA AGGAGCCTGA 9240
TGAAATCCAA AAGACATTCA ATCCTTTTTT TTAATTGGT GTTGCACATA GTTAAAAAGA 9300
TTCCATACAT TGGAAAAA AACTTCAGAG ATGTTTACAA AATGGTAACA GAATAAATG 9360

5 TGGAAACAAT AAATGTAATA ATGATTGTGA ATGTTTTTAAA AGATGGATTA CACAAAAAAA 9420
AGACGAATGG GGGAAAATAG TACAACATTT TAAAACGCAA AATATTAAAG GTAGAGGAGG 9480
TAGTGACAAT ACGGCAGAAT TAATCCCATT TGATCAGCAT TATGTTCTTC AATACAATTT 9540
GCAAGAAGAA TTTTGTAAAG GCGATTCCGA AGACGCTTCC GAAGAAAAAT CCGAAAATAG 9600
TCTGGATGCA GAGGAGGCAG AGGAACTAAA ACACCTTCGC GAAATCATTG AAAGTGAAGA 9660
CAATAATCAA GAAGCATCTG TTGGTGGTGG CGTCACTGAA CAAAAAATA TAATGGATAA 9720
ATTGCTCAAC TACGAAAAAG ACGAAGCCGA TTTATGCCTA GAAATTCACG AAGATGAGGA 9780
AGAGGAAAAA GAAAAAGGAG ACGGAAACGA ATGTATCGAA GAGGGCGAAA ATTTTCGTTA 9840
TAATCCATGT AGTGGCGAAA GTGGTAACAA ACGATACCCC GTTCTTGCGA ACAAAGTAGC 9900
10 GTATCAAATG CATCACAAGG CAAAGACACA ATTGGCTAGT CGTGCTGGTA GAAGTGCCTT 9960
GAGAGGTGAT ATATCCTTAG CGCAATTTAA AAATGGTCGT AACGGAAGTA CATTGAAAAG 10020
ACAAATTTGC AAAATTAACG AAAACTATTC CAATGATAGT CGTGGTAATA GTGGTGGACC 10080
ATGTACAGGC AAAGATGGAG ATCAGCGAGG TGTGCGCATG AGAATAGGAA CGGAATGGTC 10140
AAATATTGAA GGAAAAAACC AAACGTCATA CAAAAACGTC TTTTACCTC CCCGACGAGA 10200
15 ACACATGTGT ACATCCAATT TAGAAAATTT AGATGTTGGT AGTGTCACTA AAAATGATAA 10260
GGCTAGCCAC TCATTATTGG GAGATGTTCA GCTCGCAGCA AAACTGATG CAGCTGAGAT 10320
AATAAAACGC TATAAAGATC AAAATAATAT ACAACTAAT GATCCAATAC AACAAAAAGA 10380
CCAGGAGGCT ATGTGTGCGAG CTGTACGTTA TAGTTTTGCC GATTTAGGAG ACATTATTCG 10440
AGGAAGAGAT ATGTGGGATG AGGATAAGAG CTCAACAGAC ATGGAAACAC GTTTGATAAC 10500
20 CGTATTTTAAA AACATTAAAG AAAAACATGA TGGAAATCAA GACAACCCTA AATATACCGG 10560
TGATGAAAGC AAAAAGCCCC CATATAAAAA ATTACGAGCA GATTGGTGGG AAGCAAATAG 10620
ACATCAAGTG TGGAGAGCCA TGAATGCGC AACAAAAAGG ATCATATGTC ETGGTATGEC 10680
AGTTGACGAT TATATCCCC AACGTTTACG CTGGTAGACT GAATGGGCTG AATGGTATTG 10740
TAAAGCGCAA TCACAGGAGT ATGACAAGTT AAAAAAATC TGTGCAGATT GTATGAGTAA 10800
25 GGGTGATGGA AAATGTACGC AAGGTGATGT CGATTGTGGA AAGTGCAAAG CAGCATGTGA 10860
TAAATATAAA GAGGAAATAG AAAAATGGAA TGAACAATGG AGAAAAATAT CAGATAAATA 10920
CAATCTATTA TACCTACAAG CAAAAACTAC TTCTACTAAT CCTGGCCGTA CTGTTCTTGG 10980
TGATGACGAT CCCGACTATC AACAAATGGT AGATTTTTTTG ACCCCAATAC ACAAAGCAAG 11040
TATTGCCGCA CGTGTTCTTG TTAACCGTGC TGCTGGTAGT CCCACTGAGA TCGCCGCCCG 11100
30 CGCCCCGATC ACCCCCTACA GTACTGCTGC CGGATATATA CACCAGGAAA CATTGATAGG 11160
GGGGTGCCAG GAACAAACAC AATTTTGTGA AAAAAACAT GGTGCAACAT CAACTAGTAC 11220
CACGAAAGAA AACAAAGAAT ACACCTTTAA ACAACCTCCG CCGGAGTATG CTACAGCGTG 11280
TGATTGCATA AATAGGTCGC AAACAGAGGA GCCGAAGAAA AAGGAAGAAA ATGTAGAGAG 11340
TGCCTGCAAA ATAGTGGAGA AAATACTTGA GGGTAAGAAT GGAAGGACTA CAGTAGGTGA 11400
35 ATGTAATCCA AAGAGAGTT ATCTGATTG GGATTGCAAA AACAATATTG ACATTAGTCA 11460
TGATGGTGCT TGTATGCCTC CAAGGAGACA AAAACTATGT TTATATTATA TAGCATTGA 11520
GAGTCAAACA GAAAATATAA AAACAGACGA TAATTTGAAA GATGCTTTTA TTAATACTGC 11580
AGCAGCAGAA ACTTTTCTTT CATGGCAATA TTATAAGAGT AAGAATGATA GTGAAGCTAA 11640
AATATTAGAT AGAGGCCTTA TTCCATCCCA ATTTTAAAGA TCCATGATGT ACACGTTTGG 11700
40 AGATTATAGA GATATATGTT TGAACACAGA TATATCTAAA AAACAAAATG ATGTAGCTAA 11760
GGCAAAAGAT AAAATAGGTA AATTTTCTC AAAAGATGGC AGCAAATCTC CTAGTGGCTT 11820
ATCACGCCAA GAATGGTGGG AAACAAATGG TCCAGAGATT TGGAAAGGAA TGGTATGTGC 11880
CTTAACAAAA TACGTCACAG ATACCGATAA CAAAAGAAAA ATCAAAAACG ACTACTCATA 11940
CGATAAAGTC AACCAATCCC AAAATGGCAA CCCTTCCCTT GAAGAGTTTG CTGCTAAACC 12000
45 TCAATTTCTA CGTTGGATGA TCGAATGGGG AGAAGAGTTT TGTGCTGAAC GTCAGAGAA 12060
GGAAAATATC ATAAAAGATG CATGTAATGA AATAAATTCT ACACAACAGT GTAATGATGC 12120
GAAACATCGT TGTAATCAAG CATGTAGAGC ATATCAAGAA TATGTTGAAA ATAAAAAAA 12180
AGAATTTTCG GGACAAACAA ATAACCTTGT TCTAAAGGCA AATGTTGAGC CCAAAGATCC 12240
AGAATATAAA GGATATGAAT ATAAAGACGG CGTACAACCG ATACAGGGGA ATGAGTATTT 12300
50 ACTGCAAAAA TGTGATAATA ATAAATGTTT TTGCATGGAT GGAAATGTAC TTTCCGTCTC 12360
TCCAAAAGAA AAACCTTTTG GAAAATATGC CCATAAATAT CCTGAGAAAT GTGATTGTTA 12420
TCAAGGAAAA CATGTACCTA GCATACCACC TCCCCCCCCA CCTGTACAAC CACAACCGGA 12480
AGCACCAACA GTAACAGTAG ACGTTTGCAG CATAGTAAAA ACACTATTTA AAGACACAAA 12540
CAATTTTTCG GACGCTTG TGCTAAAATA CGGCAAAACC GCACCATCCA GTTGGAAATG 12600
55 TATACCAAGT GACACAAAA GTGGTGCTGG TGCCACCACC GGCAAAAGTG GTAGTGATAG 12660
TGGTAGTATT TGTATCCAC CCAGGAGGCG ACGATTATAT GTGGGGAAC TACAGGAGTG 12720
GGCTACCGCG CTCCCACAAG GTGAGGCGCG CGCGCCGTCC CACTCACGCG CCGACGACTT 12780
GCGCAATGCG TTCATCCAAT CTGCTGCAAT AGAGACTTTT TTCTTATGGG ATAGATATAA 12840
AGAAGAGAAA AAACCAAGG GTGATGGGTC ACAACAAGCA CTATCACAAC TAACCACTAG 12900
60 ATACAGTGAT GACGAGGAGG ACCCCCCCGA CAACTGTTA CAAAATGGTA AGATACCCCC 12960
CGATTTTTTTG AGATTAATGT TCTATACATT AGGAGATTAT AGGGATATTT TAGTACACGG 13020
TGGTAACACA AGTGACAGTG GTAACACAAA TGGTAGTAAC AACAACAATA TTGTGCTTGA 13080
AGCGAGTGGT AACAGGAGG ACATGCAAAA AATACAAGAG AAAATAGAAC AAATTCTCCC 13140
AAAAAATGGT GGCACACCTC TTGTCCCAA ATCTAGTGCC CAAACACCTG ATAAATGGTG 13200

GAATGAACAC GCCGAATCTA TCTGGAAAGG TATGATATGT GCATTGACAT ATACAGAAAA 13260
GAACCCCTGAC ACCAGTGCAG GAGGCGACGA AAACAAAATA GAAAAGGATG ATGAAGTGTA 13320
CGAGAAATTT TTTGGCAGCA CAGCCGACAA ACATGGCACA GCCTCAACCC CAACCGGCAC 13380
5 ATACAAAACC CAATACGACT ACGAAAAAGT CAAACTTGAG GATACAAGTG GTGCCAAAAC 13440
CCCCCTCAGCC TCTAGTGATA CACCCCTTCT CTCCGATTTT GTGTTACGCC CCCCCTACTT 13500
CCGTTACCTT GAAGAATGGG GTCAAAATTT TTGTAAAAAA AGAAAGCATA AATTGGCACA 13560
AATAAAACAT GAGTGTAAG TAGAAGAAAA TGGTGGTGGT AGTCGTCGTG GTGGTATAAC 13620
AAGACAATAT AGTGGGGATG GCGAAGCGTG TAATGAGATG CTTCCAAAAA ACGATGGAAC 13680
10 TGTTCCGGAT TTAGAAAAGC CGAGTTGTGC CAAACCTTGT AGTTCTTATA GAAAATGGAT 13740
AGAAAGCAAG GGAAGTAATA AGCATGATA TGGATTTTGT GAAACACTAA CAACGTCCTC 13800
ATGTGTAAAT GGAAGTAATA AGCATGATA TGGATTTTGT GAAACACTAA CAACGTCCTC 13860
TAAAGCTAAA GACTTTTTTA AAACGTTAGG ACCATGTAAA CCTAATAATG TAGAGGGTAA 13920
AACAATTTTT GATGATGATA AAACCTTTAA ACATACAAAA GATTGTGATC CATGCTTAA 13980
ATTTAGTGTT AATTGTAAAA AAGATGAATG TGATAATTCT AAAGGAACCG ATTGCCGAAA 14040
15 TAAAATAGT ATTGATGCAA CAGATATTGA AAATGGAGTG GATTCTACTG TACTAGAAAT 14100
GCGTGTAGT GCTGATAGTA AAAGTGGATT TAATGGTGAT GGTTTAGAGA ATGCTTGATG 14160
AGGTGCTGGT ATCTTTGAAG GTATTAGAAA AGATGAATGG AAATGTCGTA ATGTATGTGG 14220
TTATGTTGTA TGTAACCCGG AAAACGTTAA TGGGGAAGCA AAGGGAAAAA ACATTATACA 14280
AATTAGAGCA CTGGTTAAAC GTTGGGTAGA ATATTTTTTT GAAGATTATA ATAAAAATA 14340
20 ACATAAAATT TCACATCGCA TAAAAAATGG TGAAATATCT CCATGTATAA AAAATTGTGT 14400
AGAAAAATGG GTAGATCAGA AAAGAAAAGA ATGGAAGGAA ATTACTGAAC GTTTCAAAGA 14460
TCAATATAAA AATGACAATT CAGATGATGA CAATGTGAGA AGTTTTTTGG AGACCTTGAT 14520
ACCTCAAATT ACTGATGCAA ACGCTAAAA TAAGGTATA AAATTAAGTA AGTTCGGTAA 14580
TTCTTGTTGA TGTAAGTCCA GTGCGAAGCA ACAAACAAA AATGGTGAAT ACAAGGACGC 14640
25 TATAGATTGT ATGCTTAAAA AGCTTAAAGA TAAAATTGGC GAGTGCGAAA AGAAACACCA 14700
TCAAACAGT GATACCGAGT GTTCCGACAC ACCACAACCG CAAACCCCTG AAGACGAAAC 14760
TTTGATGAT GATATAGAAA CAGAGGAGGC GAAGAAGAAC ATGATGCCGA AAATTTGTGA 14820
AAATGTGTTA AAAACAGCAC AACAAGAGGA TGAAGGCGGT TGTGTCCCAG CAGAAAATAG 14880
TGAAGAACCG GCAGCAACAG ATAGTGGTAA GGAAACCCCG GAACAAACCC CCGTTCTCAA 14940
30 ACCCGAAGAA GAAGCAGTAC CGGAACCCAC ACCTCCACCC CCACAGGAAA AAGCCCCGGC 15000
ACCAATACCC CAACCACAAC CACCAACCCC CCCACACAA CTCTTGGATA ATCCCCAGT 15060
TCTAACCGCC CTGGTGACCT CCACCCTCGC CTGGAGCGTT GGCATCGGTT TTGCTACATT 15120
CACTTATTTT TATCTAAAGG TAAATGGAAG TATATATATG GGGATGTGGA TGTATGTGGA 15180
TGATGTGTTA TGTATGTGGA TGTATGTGGA TGTATGTGGA TGTGTTTTAT GGATATGTAT 15240
35 TTGTGATTAT GTTTGGATAT ATATATATAT ATATATATAT TTATGTATAT GTGTTTTTGG 15300
ATATATATAT GTGTATGTAT ATGATTTTCT GTATATGTAT TTGTGGGTTA AGGATATATA 15360
TATATGGATG TACTTGTATG TGTTTTATAT ATATATTTTA TATATATGTA TTTATATATA 15420
AAAAGAAATA TAAAAACAAA TTTATTAAAA TGAAAAAAG AAAAATGAAA TATAAAAAAA 15480
AATTTATTAA AATAAAAAAA AAAAAAATA AAAAGGAGAA AAATTTTTTA AAAAATAATA 15540
40 AAAATATATA TAAAATATA ATTTTGATAG AATAAAAAAT GAAAAAGATT ATCAAAAAAA 15600
AATTAATAAA AAATTTTATA TAAAAAATA ATGATTATA AAAAAATAA AACAAAAGAA 15660
GAAAAAATAA AACATTAAAA AAAAAAATA ATATATCATA AAAACAAAAA AAAAGAAAAA 15720
AAATATATTA AAATAAAAAAT ATATATCATA AAATAAAAAA AAATTAATAA AATGTTAAAA 15780
AAAAAATATA TACATAAAAT AAAAAAATA TATTTAAATA AAAAAAATA ATAAATAAAA 15840
45 AAATTTAATT AAATAAAAAA AAATAATAA TAAAAAATT TAATTAATAA AAAAAAATT 15900
AAAAAATTT AATGAAATAA AAAAAATAA AAAAATTTAA TTAATAAAA AAAATAAAAT 15960
AAAATTAATT ACATGCACAT ATACATACAT ATATATATAT ATATACCAT AACTACATAC 16020
AACATTTACA CATACATATA TATATATATA TATACCCATA ACTACATACA CATTACATA 16080
50 TACATATATA TATTATATAT ATATATATAT ATACCCATA CTACATACAT ATATACATTA 16140
ACAAACACAT ATATAATACC TAAATACATA TATACATACA CATATATGTT CATTTTTTTT 16200
TTTAGAAAAA AACCAAATCA TCTGTTGGAA ATTTATTCCA AATACTGCAA ATACCCAAAA 16260
GTGATTATGA TATACCGACA AAACCTTCAC CCAATAGATA TATACCTTAT ACTAGTGGTA 16320
AATACAGAGG CAAACGGTAC ATTTACCTTG AAGGAGATAG TGAACAGAT AGTGGTTACA 16380
CCGATCATT TAGTGATATA ACTTCCTCAG AAAGTGAATA TGAAGAGATG GATATAAATG 16440
55 ATATATATGT ACCAGGTAGT CCTAAATATA AAACATTAAT TGAAGTGGTA CTTGAACCTA 16500
GTGGTAACAA CACAACAGCT AGTGGTAACA ACACAACAGC TAGTGGTAAC AACACAACAG 16560
CTAGTGGTAA AAACACACCT AGTGATACAC AAAATGATAT ACAAAATGAT GGTATACCTA 16620
GTAGTAAAT TACAGATAAT GAATGGAATC AATTGAAAGA TGAATTTATA TCACAATATC 16680
TACAAAGTGA ACCAAATACA GAACCAATA TGTTAGGTTA TAATGTGGAT AATAATACCC 16740
60 ATCTTACCAC GTCACATCAT AATGTGGAAG AAAACCTTT TATTATGTCC ATTCATGATA 16800
GAAATTTATT TAGTGGAGAA GAATACAATT ATGATATGTT TAATAGTGGG AATAATCCAA 16860
TAAACATTAG TGATTCAACA AATAGTATGG ATAGTCTAAC AAGTAACAAC CATAGTCCAT 16920
ATAATGATAA AAATGATTTA TATAGTGGTA TCGACCTAAT CAACGACGCA CTAAGTGGTA 16980
ATCATATTGA TATATATGAT GAAATGCTCA AACGAAAAGA AAATGAATTA TTTGGAACAA 17040
65 AACATCATAC AAAACATACA AATACATATA ATGTCGCCAA ACCTGCACGT GACGACCCTA 17100

TAACCAATCA AATAAATTTG TTCCATAAAT GGTTAGATAG GCATAGAGAT ATGTGCGAAA 17160
 AGTGGAAGAA TAATCACGAA CGGTTACCCA AATTGAAAGA ATTGTGGGAA AATGAGACAC 17220
 ATAGTGGTGA CATAAATAGT GGTATACCTA GTGGTAACCA TGTGTTGAAT ACTGATGTTT 17280
 CTATTCAAAT AGATATGGAT AATCCTAAAA CAAAGAATGA AATTACGAAT ATGGATACAA 17340
 5 ACCCAGACAA ATCTACTATG GATACTATAC TGGATGATCT GGAAAAATAT AATGAACCCT 17400
 ACTACTATGA TTTTATGAA GATGATATCA TCTATCATGA TGTAGATGTT GAAAAATCAT 17460
 CTATGGATGA TATATATGTG GATCATAATA ATGTGACTAA TAATAATATG GATGTACCTA 17520
 CTAAGATGCA CATCGAAATG AATATTGTTA ATAATAAAAA GGAGATTTTC GAAGAGGAAT 17580
 ATCCTATATC AGATATATGG AATATCTAAA ATTAATATAC TTTTATTTGTG TGTGTCATAT 17640
 10 ATATTTTGTG TTATTTGTAT ATGTTTTTAT TTTATTTATT TATTATTATTA TTTATTGTTT 17700
 TTGGTATATT TGTAAGAAAT ATGTTTTTGT TTATAATCAT ATTATTATAT TTTAATAAT 17760
 TTGCAACATG ATTTTTTTTT TTCTTCTTA TTGTGTAATT TTTTTCATAA TATTTATATA 17820
 TATATATGTA TTTTATTTT TAGTATAATA ATTGTATCTA TATTTGATTA ATAATTATGT 17880
 ATATTATGGT TATTTTGTGTT CTTTTCTGT ACATTTTTTC GTAATATATA TATATATATA 17940
 15 TATATATAAT TCTCTTTTTC TAATATATAT ATCCTTCTAT TTTCGATTTT TTCATTTTTT 18000
 TCCAGTATTA ATTTATTTAT TTATTTGTGA TATTTTATAA TATATTATTT AAATGTGTAT 18060
 TTATATATGT GTTTTATATA TGTGTTTTAT TTTTGTACT CTAATTCTGA ATAATCCGAG 18120
 CGAAAAAATA ATATATAATC TCATATAAAA ATTATTTATA ATACAATATT ATATAGTTTC 18180
 CTATTAAAAA AAATTAATAT AATATACAAT AATATTTCTT GTTATTTTTA TAAATATAAC 18240
 20 TAATTTCTTA TTTTATTTA ACTTTATTC TTTTAAATT CTTAATTCTT TTATCAAACA 18300
 AAAACATAA AGTAATTCTA CATATCAACA AAAAAAAAAA AAAAAAAAAA AAAAAAATT 18360
 TATTATAATA TAATAAAAAA TATAAGACA TAGGTTGACT TATTTATTATA AATGATTTAT 18420
 TACGATTAAA ACATATTGAG ATTATAATAA TATAATTTAA CATAGAAAGA GTTAAGAATA 18480
 CATTTTTTTT TTTATTTTGA TATGTAATTC AACATATATA TATATATATA TCTTTTAAAT 18540
 25 TTAATTAAAT AAAATTCCTT ATTATTCATA TTGTTTCTTT TATCACATGT GAAATATTAA 18600
 AAATAATTTT CGATTTTATC GATATATTTA TGTCGTTTAT ATACTTATAT AGGTCTTTAT 18660
 AACTATTGAT TAATAGAAGG TAATAGCCTA ATAATATAAA TACTCGTATT TATAAATTCA 18720
 TTTATATATT TCAAATATAT TTGCATGGTT TATTTTCAAA TACAATTAAT TAGATTTCTT 18780
 AAATATTTCT TCATTTATTC ATTTTATAG CATATACATG CACATTATAA ATTATTATA 18840
 30 AAAAATTTT ATTTAATAT ATAATAACA TTTTCATACA TTACATTTT CACACAACAT 18900
 TTAAGTTGTC ATAATGTAAC ACATTAAATA ATATATTACT TATATATATA TAATTATTAA 18960
 TTATATATTA AATAAAATG TATTATCGCC TGTATTATCA TAGTATATAT AATGTTGTAT 19020
 AACGCTTCAA AATATATATA ATAATATAAT TAAAAATATA TATATAGTAA TTAATTATTT 19080
 TGTATGTTA TGTAATAATG CAATTAATAT AAGATAAAAT TCAT 19124

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 3060 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Met Val Glu Leu Ala Lys Met Gly Pro Lys Glu Ala Ala Gly Gly Asp
 1 5 10 15
 50 Asp Ile Glu Asp Glu Ser Ala Lys His Met Phe Asp Arg Ile Gly Lys
 20 25 30
 Asp Val Tyr Asp Lys Val Lys Glu Ala Lys Glu Arg Gly Lys Gly
 35 40 45
 55 Leu Gln Gly Arg Leu Ser Glu Ala Lys Phe Glu Lys Asn Glu Ser Asp
 50 55 60
 Pro Gln Thr Pro Glu Asp Pro Cys Asp Leu Asp His Lys Tyr His Thr
 65 70 75 80
 Asn Val Thr Thr Asn Val Ile Asn Pro Cys Ala Asp Arg Ser Asp Val
 85 90 95
 60 Arg Phe Ser Asp Glu Tyr Gly Gly Gln Cys Thr His Asn Arg Ile Lys
 100 105 110
 Asp Ser Gln Gln Gly Asp Asn Lys Gly Ala Cys Ala Pro Tyr Arg Arg
 115 120 125
 65 Leu His Val Cys Asp Gln Asn Leu Glu Gln Ile Glu Pro Ile Lys Ile
 130 135 140

Thr Asn Thr His Asn Leu Leu Val Asp Val Cys Met Ala Ala Lys Phe
 145 150 155 160
 Glu Gly Gln Ser Ile Thr Gln Asp Tyr Pro Lys Tyr Gln Ala Thr Tyr
 165 170 175
 Gly Asp Ser Pro Ser Gln Ile Cys Thr Met Leu Ala Arg Ser Phe Ala
 180 185 190
 Asp Ile Gly Asp Ile Val Arg Gly Arg Asp Leu Tyr Leu Gly Asn Pro
 195 200 205
 Gln Glu Ile Lys Gln Arg Gln Gln Leu Glu Asn Asn Leu Lys Thr Ile
 210 215 220
 Phe Gly Lys Ile Tyr Glu Lys Leu Asn Gly Ala Glu Ala Arg Tyr Gly
 225 230 235 240
 Asn Asp Pro Glu Phe Phe Lys Leu Arg Glu Asp Trp Trp Thr Ala Asn
 245 250 255
 Arg Glu Thr Val Trp Lys Ala Ile Thr Cys Asn Ala Trp Gly Asn Thr
 260 265 270
 Tyr Phe His Ala Thr Cys Asn Arg Gly Glu Arg Thr Lys Gly Tyr Cys
 275 280 285
 Arg Cys Asn Asp Asp Gln Val Pro Thr Tyr Phe Asp Tyr Val Pro Gln
 290 295 300
 Tyr Leu Arg Trp Phe Glu Glu Trp Ala Glu Asp Phe Cys Arg Lys Lys
 305 310 315 320
 Asn Lys Lys Ile Lys Asp Val Lys Arg Asn Cys Arg Gly Lys Asp Lys
 325 330 335
 Glu Asp Lys Asp Arg Tyr Cys Ser Arg Asn Gly Tyr Asp Cys Glu Lys
 340 345 350
 Thr Lys Arg Ala Ile Gly Lys Leu Arg Tyr Gly Lys Gln Cys Ile Ser
 355 360 365
 Cys Leu Tyr Ala Cys Asn Pro Tyr Val Asp Trp Ile Asn Asn Gln Lys
 370 375 380
 Glu Gln Phe Asp Lys Gln Lys Lys Lys Tyr Asp Glu Glu Ile Lys Lys
 385 390 395 400
 Tyr Glu Asn Gly Ala Ser Gly Gly Ser Arg Gln Lys Arg Asp Ala Gly
 405 410 415
 Gly Thr Thr Thr Thr Asn Tyr Asp Gly Tyr Glu Lys Lys Phe Tyr Asp
 420 425 430
 Glu Leu Asn Lys Ser Glu Tyr Arg Thr Val Asp Lys Phe Leu Glu Lys
 435 440 445
 Leu Ser Asn Glu Glu Ile Cys Thr Lys Val Lys Asp Glu Glu Gly Gly
 450 455 460
 Thr Ile Asp Phe Lys Asn Val Asn Ser Asp Ser Thr Ser Gly Ala Ser
 465 470 475 480
 Gly Thr Asn Val Glu Ser Gln Gly Thr Phe Tyr Arg Ser Lys Tyr Cys
 485 490 495
 Gln Pro Cys Pro Tyr Cys Gly Val Lys Lys Val Asn Asn Gly Gly Ser
 500 505 510
 Ser Asn Glu Trp Glu Glu Lys Asn Asn Gly Lys Cys Lys Ser Gly Lys
 515 520 525
 Leu Tyr Glu Pro Lys Pro Asp Lys Glu Gly Thr Thr Ile Thr Ile Leu
 530 535 540
 Lys Ser Gly Lys Gly His Asp Asp Ile Glu Glu Lys Leu Asn Lys Phe
 545 550 555 560
 Cys Asp Glu Lys Asn Gly Asp Thr Ile Asn Ser Gly Gly Ser Gly Thr
 565 570 575
 Gly Gly Ser Gly Gly Gly Asn Ser Gly Arg Gln Glu Leu Tyr Glu Glu
 580 585 590
 Trp Lys Cys Tyr Lys Gly Glu Asp Val Val Lys Val Gly His Asp Glu
 595 600 605
 Asp Asp Glu Glu Asp Tyr Glu Asn Val Lys Asn Ala Gly Gly Leu Cys
 610 615 620
 Ile Leu Lys Asn Gln Lys Lys Asn Lys Glu Glu Gly Gly Asn Thr Ser
 625 630 635 640
 Glu Lys Glu Pro Asp Glu Ile Gln Lys Thr Phe Asn Pro Phe Phe Tyr
 645 650 655
 Tyr Trp Val Ala His Met Leu Lys Asp Ser Ile His Trp Lys Lys Lys

				660					665					670					
				Leu	Gln	Arg	Cys	Leu	Gln	Asn	Gly	Asn	Arg	Ile	Lys	Cys	Gly	Asn	Asn
				675							680					685			
5				Lys	Cys	Asn	Asn	Asp	Cys	Glu	Cys	Phe	Lys	Arg	Trp	Ile	Thr	Gln	Lys
				690						695					700				
				Lys	Asp	Glu	Trp	Gly	Lys	Ile	Val	Gln	His	Phe	Lys	Thr	Gln	Asn	Ile
				705				710						715				720	
				Lys	Gly	Arg	Gly	Gly	Ser	Asp	Asn	Thr	Ala	Glu	Leu	Ile	Pro	Phe	Asp
								725					730					735	
10				His	Asp	Tyr	Val	Leu	Gln	Tyr	Asn	Leu	Gln	Glu	Glu	Phe	Leu	Lys	Gly
				740							745						750		
				Asp	Ser	Glu	Asp	Ala	Ser	Glu	Glu	Lys	Ser	Glu	Asn	Ser	Leu	Asp	Ala
				755						760						765			
15				Glu	Glu	Ala	Glu	Glu	Leu	Lys	His	Leu	Arg	Glu	Ile	Ile	Glu	Ser	Glu
				770					775						780				
				Asp	Asn	Asn	Gln	Glu	Ala	Ser	Val	Gly	Gly	Gly	Val	Thr	Glu	Gln	Lys
				785				790						795				800	
				Asn	Ile	Met	Asp	Lys	Leu	Leu	Asn	Tyr	Glu	Lys	Asp	Glu	Ala	Asp	Leu
				805								810						815	
20				Cys	Leu	Glu	Ile	His	Glu	Asp	Glu	Glu	Glu	Glu	Lys	Glu	Lys	Gly	Asp
				820								825					830		
				Gly	Asn	Glu	Cys	Ile	Glu	Glu	Gly	Glu	Asn	Phe	Arg	Tyr	Asn	Pro	Cys
				835							840					845			
25				Ser	Gly	Glu	Ser	Gly	Asn	Lys	Arg	Tyr	Pro	Val	Leu	Ala	Asn	Lys	Val
				850					855						860				
				Ala	Tyr	Gln	Met	His	His	Lys	Ala	Lys	Thr	Gln	Leu	Ala	Ser	Arg	Ala
				865				870						875				880	
				Gly	Arg	Ser	Ala	Leu	Arg	Gly	Asp	Ile	Ser	Leu	Ala	Gln	Phe	Lys	Asn
								885					890					895	
30				Gly	Arg	Asn	Gly	Ser	Thr	Leu	Lys	Gly	Gln	Ile	Cys	Lys	Ile	Asn	Glu
				900								905						910	
				Asn	Tyr	Ser	Asn	Asp	Ser	Arg	Gly	Asn	Ser	Gly	Gly	Pro	Cys	Thr	Gly
				915							920					925			
35				Lys	Asp	Gly	Asp	His	Gly	Gly	Val	Arg	Met	Arg	Ile	Gly	Thr	Glu	Trp
				930					935						940				
				Ser	Asn	Ile	Glu	Gly	Lys	Lys	Gln	Thr	Ser	Tyr	Lys	Asn	Val	Phe	Leu
				945				950						955				960	
				Pro	Pro	Arg	Arg	Glu	His	Met	Cys	Thr	Ser	Asn	Leu	Glu	Asn	Leu	Asp
								965					970					975	
40				Val	Gly	Ser	Val	Thr	Lys	Asn	Asp	Lys	Ala	Ser	His	Ser	Leu	Leu	Gly
				980								985					990		
				Asp	Val	Gln	Leu	Ala	Ala	Lys	Thr	Asp	Ala	Ala	Glu	Ile	Ile	Lys	Arg
				995							1000					1005			
45				Tyr	Lys	Asp	Gln	Asn	Asn	Ile	Gln	Leu	Thr	Asp	Pro	Ile	Gln	Gln	Lys
				1010					1015						1020				
				Asp	Gln	Glu	Ala	Met	Cys	Arg	Ala	Val	Arg	Tyr	Ser	Phe	Ala	Asp	Leu
				1025				1030						1035				1040	
				Gly	Asp	Ile	Ile	Arg	Gly	Arg	Asp	Met	Trp	Asp	Glu	Asp	Lys	Ser	Ser
								1045					1050					1055	
50				Thr	Asp	Met	Glu	Thr	Arg	Leu	Ile	Thr	Val	Phe	Lys	Asn	Ile	Lys	Glu
				1060								1065						1070	
				Lys	His	Asp	Gly	Ile	Lys	Asp	Asn	Pro	Lys	Tyr	Thr	Gly	Asp	Glu	Ser
				1075						1080						1085			
55				Lys	Lys	Pro	Ala	Tyr	Lys	Lys	Leu	Arg	Ala	Asp	Trp	Trp	Glu	Ala	Asn
				1090						1095					1100				
				Arg	His	Gln	Val	Trp	Arg	Ala	Met	Lys	Cys	Ala	Thr	Lys	Gly	Ile	Ile
				1105				1110						1115				1120	
				Cys	Pro	Gly	Met	Pro	Val	Asp	Asp	Tyr	Ile	Pro	Gln	Arg	Leu	Arg	Trp
								1125					1130					1135	
60				Met	Thr	Glu	Trp	Ala	Glu	Trp	Tyr	Cys	Lys	Ala	Gln	Ser	Gln	Glu	Tyr
				1140								1145						1150	
				Asp	Lys	Leu	Lys	Lys	Ile	Cys	Ala	Asp	Cys	Met	Ser	Lys	Gly	Asp	Gly
				1155						1160						1165			
65				Lys	Cys	Thr	Gln	Gly	Asp	Val	Asp	Cys	Gly	Lys	Cys	Lys	Ala	Ala	Cys
				1170						1175						1180			

Asp Lys Tyr Lys Glu Glu Ile Glu Lys Trp Asn Glu Gln Trp Arg Lys
 1185 1190 1195 1200
 Ile Ser Asp Lys Tyr Asn Leu Leu Tyr Leu Gln Ala Lys Thr Thr Ser
 1205 1210 1215
 Thr Asn Pro Gly Arg Thr Val Leu Gly Asp Asp Asp Pro Asp Tyr Gln
 1220 1225 1230
 Gln Met Val Asp Phe Leu Thr Pro Ile His Lys Ala Ser Ile Ala Ala
 1235 1240 1245
 Arg Val Leu Val Lys Arg Ala Ala Gly Ser Pro Thr Glu Ile Ala Ala
 1250 1255 1260
 Ala Ala Pro Ile Thr Pro Tyr Ser Thr Ala Ala Gly Tyr Ile His Gln
 1265 1270 1275 1280
 Glu Ile Gly Tyr Gly Gly Cys Gln Glu Gln Thr Gln Phe Cys Glu Lys
 1285 1290 1295
 Lys His Gly Ala Thr Ser Thr Ser Thr Thr Lys Glu Asn Lys Glu Tyr
 1300 1305 1310
 Thr Phe Lys Gln Pro Pro Pro Glu Tyr Ala Thr Ala Cys Asp Cys Ile
 1315 1320 1325
 Asn Arg Ser Gln Thr Glu Glu Pro Lys Lys Lys Glu Glu Asn Val Glu
 1330 1335 1340
 Ser Ala Cys Lys Ile Val Glu Lys Ile Leu Glu Gly Lys Asn Gly Arg
 1345 1350 1355 1360
 Thr Thr Val Gly Glu Cys Asn Pro Lys Glu Ser Tyr Pro Asp Trp Asp
 1365 1370 1375
 Cys Lys Asn Asn Ile Asp Ile Ser His Asp Gly Ala Cys Met Pro Pro
 1380 1385 1390
 Arg Arg Gln Lys Leu Cys Leu Tyr Thr Ile Ala His Glu Ser Gln Thr
 1395 1400 1405
 Glu Asn Ile Lys Thr Asp Asp Asn Leu Lys Asp Ala Phe Ile Lys Thr
 1410 1415 1420
 Ala Ala Ala Glu Thr Phe Leu Ser Trp Gln Tyr Tyr Lys Ser Lys Asn
 1425 1430 1435 1440
 Asp Ser Glu Ala Lys Ile Leu Asp Arg Gly Leu Ile Pro Ser Gln Phe
 1445 1450 1455
 Leu Arg Ser Met Met Tyr Thr Phe Gly Asp Tyr Arg Asp Ile Cys Leu
 1460 1465 1470
 Asn Thr Asp Ile Ser Lys Lys Gln Asn Asp Val Ala Lys Ala Lys Asp
 1475 1480 1485
 Lys Ile Gly Lys Phe Phe Ser Lys Asp Gly Ser Lys Ser Pro Ser Gly
 1490 1495 1500
 Leu Ser Arg Gln Glu Trp Trp Lys Thr Asn Gly Pro Glu Ile Trp Lys
 1505 1510 1515 1520
 Gly Met Leu Cys Ala Leu Thr Lys Tyr Val Thr Asp Thr Asp Asn Lys
 1525 1530 1535
 Arg Lys Ile Lys Asn Asp Tyr Ser Tyr Asp Lys Val Asn Gln Ser Gln
 1540 1545 1550
 Asn Gly Asn Pro Ser Leu Glu Glu Phe Ala Ala Lys Pro Gln Phe Leu
 1555 1560 1565
 Arg Trp Met Ile Glu Trp Gly Glu Glu Phe Cys Ala Glu Arg Gln Lys
 1570 1575 1580
 Lys Glu Asn Ile Ile Lys Asp Ala Cys Asn Glu Ile Asn Ser Thr Gln
 1585 1590 1595 1600
 Gln Cys Asn Asp Ala Lys His Arg Cys Asn Gln Ala Cys Arg Ala Tyr
 1605 1610 1615
 Gln Glu Tyr Val Glu Asn Lys Lys Lys Glu Phe Ser Gly Gln Thr Asn
 1620 1625 1630
 Asn Phe Val Leu Lys Ala Asn Val Gln Pro Gln Asp Pro Glu Tyr Lys
 1635 1640 1645
 Gly Tyr Glu Tyr Lys Asp Gly Val Gln Pro Ile Gln Gly Asn Glu Tyr
 1650 1655 1660
 Leu Leu Gln Lys Cys Asp Asn Asn Lys Cys Ser Cys Met Asp Gly Asn
 1665 1670 1675 1680
 Val Leu Ser Val Ser Pro Lys Glu Lys Pro Phe Gly Lys Tyr Ala His
 1685 1690 1695
 Lys Tyr Pro Glu Lys Cys Asp Cys Tyr Gln Gly Lys His Val Pro Ser

					1700					1705					1710				
	Ile	Pro	Pro	Pro	Pro	Pro	Pro	Val	Gln	Pro	Gln	Pro	Glu	Ala	Pro	Thr			
5	Val	Thr	Val	Asp	Val	Cys	Ser	Ile	Val	Lys	Thr	Leu	Phe	Lys	Asp	Thr			
	Asn	Asn	Phe	Ser	Asp	Ala	Cys	Gly	Leu	Lys	Tyr	Gly	Lys	Thr	Ala	Pro			
	Ser	Ser	Trp	Lys	Cys	Ile	Pro	Ser	Asp	Thr	Lys	Ser	Gly	Ala	Gly	Ala			
10	Thr	Thr	Gly	Lys	Ser	Gly	Ser	Asp	Ser	Gly	Ser	Ile	Cys	Ile	Pro	Pro			
	Arg	Arg	Arg	Arg	Leu	Tyr	Val	Gly	Lys	Leu	Gln	Glu	Trp	Ala	Thr	Ala			
15	Leu	Pro	Gln	Gly	Glu	Gly	Ala	Ala	Pro	Ser	His	Ser	Arg	Ala	Asp	Asp			
	Leu	Arg	Asn	Ala	Phe	Ile	Gln	Ser	Ala	Ala	Ile	Glu	Thr	Phe	Phe	Leu			
	Trp	Asp	Arg	Tyr	Lys	Glu	Glu	Lys	Lys	Pro	Gln	Gly	Asp	Gly	Ser	Gln			
20	Gln	Ala	Leu	Ser	Gln	Leu	Thr	Ser	Thr	Tyr	Ser	Asp	Asp	Glu	Glu	Asp			
	Pro	Pro	Asp	Lys	Leu	Leu	Gln	Asn	Gly	Lys	Ile	Pro	Pro	Asp	Phe	Leu			
25	Arg	Leu	Met	Phe	Tyr	Thr	Leu	Gly	Asp	Tyr	Arg	Asp	Ile	Leu	Val	His			
	Gly	Gly	Asn	Thr	Ser	Asp	Ser	Gly	Asn	Thr	Asn	Gly	Ser	Asn	Asn	Asn			
	Asn	Ile	Val	Leu	Glu	Ala	Ser	Gly	Asn	Lys	Glu	Asp	Met	Gln	Lys	Ile			
30	Gln	Glu	Lys	Ile	Glu	Gln	Ile	Leu	Pro	Lys	Asn	Gly	Gly	Thr	Pro	Leu			
	Val	Pro	Lys	Ser	Ser	Ala	Gln	Thr	Pro	Asp	Lys	Trp	Trp	Asn	Glu	His			
35	Ala	Glu	Ser	Ile	Trp	Lys	Gly	Met	Ile	Cys	Ala	Leu	Thr	Tyr	Thr	Glu			
	Lys	Asn	Pro	Asp	Thr	Ser	Ala	Arg	Gly	Asp	Glu	Asn	Lys	Ile	Glu	Lys			
	Asp	Asp	Glu	Val	Tyr	Glu	Lys	Phe	Phe	Gly	Ser	Thr	Ala	Asp	Lys	His			
40	Gly	Thr	Ala	Ser	Thr	Pro	Thr	Gly	Thr	Tyr	Lys	Thr	Gln	Tyr	Asp	Tyr			
	Glu	Lys	Val	Lys	Leu	Glu	Asp	Thr	Ser	Gly	Ala	Lys	Thr	Pro	Ser	Ala			
45	Ser	Ser	Asp	Thr	Pro	Leu	Leu	Ser	Asp	Phe	Val	Leu	Arg	Pro	Pro	Tyr			
	Phe	Arg	Tyr	Leu	Glu	Glu	Trp	Gly	Gln	Asn	Phe	Cys	Lys	Lys	Arg	Lys			
	His	Lys	Leu	Ala	Gln	Ile	Lys	His	Glu	Cys	Lys	Val	Glu	Glu	Asn	Gly			
50	Gly	Gly	Ser	Arg	Arg	Gly	Gly	Ile	Thr	Arg	Gln	Tyr	Ser	Gly	Asp	Gly			
	Glu	Ala	Cys	Asn	Glu	Met	Leu	Pro	Lys	Asn	Asp	Gly	Thr	Val	Pro	Asp			
55	Leu	Glu	Lys	Pro	Ser	Cys	Ala	Lys	Pro	Cys	Ser	Ser	Tyr	Arg	Lys	Trp			
	Ile	Glu	Ser	Lys	Gly	Lys	Glu	Phe	Glu	Lys	Gln	Glu	Lys	Ala	Tyr	Glu			
	Gln	Gln	Lys	Asp	Lys	Cys	Val	Asn	Gly	Ser	Asn	Lys	His	Asp	Asn	Gly			
60	Phe	Cys	Glu	Thr	Leu	Thr	Thr	Ser	Ser	Lys	Ala	Lys	Asp	Phe	Leu	Lys			
	Thr	Leu	Gly	Pro	Cys	Lys	Pro	Asn	Asn	Val	Glu	Gly	Lys	Thr	Ile	Phe			
65	Asp	Asp	Asp	Lys	Thr	Phe	Lys	His	Thr	Lys	Asp	Cys	Asp	Pro	Cys	Leu			

5 Lys Phe Ser Val Asn Cys Lys Lys Asp Glu Cys Asp Asn Ser Lys Gly
 2225 2230 2235 2240
 Thr Asp Cys Arg Asn Lys Asn Ser Ile Asp Ala Thr Asp Ile Glu Asn
 2245 2250 2255
 Gly Val Asp Ser Thr Val Leu Glu Met Arg Val Ser Ala Asp Ser Lys
 2260 2265 2270
 Ser Gly Phe Asn Gly Asp Gly Leu Glu Asn Ala Cys Arg Gly Ala Gly
 2275 2280 2285
 10 Ile Phe Glu Gly Ile Arg Lys Asp Glu Trp Lys Cys Arg Asn Val Cys
 2290 2295 2300
 Gly Tyr Val Val Cys Lys Pro Glu Asn Val Asn Gly Glu Ala Lys Gly
 2305 2310 2315 2320
 Lys His Ile Ile Gln Ile Arg Ala Leu Val Lys Arg Trp Val Glu Tyr
 2325 2330 2335
 15 Phe Phe Glu Asp Tyr Asn Lys Ile Lys His Lys Ile Ser His Arg Ile
 2340 2345 2350
 Lys Asn Gly Glu Ile Ser Pro Cys Ile Lys Asn Cys Val Glu Lys Trp
 2355 2360 2365
 20 Val Asp Gln Lys Arg Lys Glu Trp Lys Glu Ile Thr Glu Arg Phe Lys
 2370 2375 2380
 Asp Gln Tyr Lys Asn Asp Asn Ser Asp Asp Asp Asn Val Arg Ser Phe
 2385 2390 2395 2400
 Leu Glu Thr Leu Ile Pro Gln Ile Thr Asp Ala Asn Ala Lys Asn Lys
 2405 2410 2415
 25 Val Ile Lys Leu Ser Lys Phe Gly Asn Ser Cys Gly Cys Ser Ala Ser
 2420 2425 2430
 Ala Asn Glu Gln Asn Lys Asn Gly Glu Tyr Lys Asp Ala Ile Asp Cys
 2435 2440 2445
 30 Met Leu Lys Lys Leu Lys Asp Lys Ile Gly Glu Cys Glu Lys Lys His
 2450 2455 2460
 His Gln Thr Ser Asp Thr Glu Cys Ser Asp Thr Pro Gln Pro Gln Thr
 2465 2470 2475 2480
 Leu Glu Asp Glu Thr Leu Asp Asp Asp Ile Glu Thr Glu Glu Ala Lys
 2485 2490 2495
 35 Lys Asn Met Met Pro Lys Ile Cys Glu Asn Val Leu Lys Thr Ala Gln
 2500 2505 2510
 Gln Glu Asp Glu Gly Gly Cys Val Pro Ala Glu Asn Ser Glu Glu Pro
 2515 2520 2525
 40 Ala Ala Thr Asp Ser Gly Lys Glu Thr Pro Glu Gln Thr Pro Val Leu
 2530 2535 2540
 Lys Pro Glu Glu Glu Ala Val Pro Glu Pro Pro Pro Pro Pro Gln
 2545 2550 2555 2560
 Glu Lys Ala Pro Ala Pro Ile Pro Gln Pro Gln Pro Pro Thr Pro Pro
 2565 2570 2575
 45 Thr Gln Leu Leu Asp Asn Pro His Val Leu Thr Ala Leu Val Thr Ser
 2580 2585 2590
 Thr Leu Ala Trp Ser Val Gly Ile Gly Phe Ala Thr Phe Thr Tyr Phe
 2595 2600 2605
 50 Tyr Leu Lys Lys Lys Thr Lys Ser Ser Val Gly Asn Leu Phe Gln Ile
 2610 2615 2620
 Leu Gln Ile Pro Lys Ser Asp Tyr Asp Ile Pro Thr Lys Leu Ser Pro
 2625 2630 2635 2640
 Asn Arg Tyr Ile Pro Tyr Thr Ser Gly Lys Tyr Arg Gly Lys Arg Tyr
 2645 2650 2655
 55 Ile Tyr Leu Glu Gly Asp Ser Gly Thr Asp Ser Gly Tyr Thr Asp His
 2660 2665 2670
 Tyr Ser Asp Ile Thr Ser Ser Glu Ser Glu Tyr Glu Glu Met Asp Ile
 2675 2680 2685
 60 Asn Asp Ile Tyr Val Pro Gly Ser Pro Lys Tyr Lys Thr Leu Ile Glu
 2690 2695 2700
 Val Val Leu Glu Pro Ser Gly Asn Asn Thr Thr Ala Ser Gly Asn Asn
 2705 2710 2715 2720
 Thr Thr Ala Ser Gly Asn Asn Thr Thr Ala Ser Gly Lys Asn Thr Pro
 2725 2730 2735
 65 Ser Asp Thr Gln Asn Asp Ile Gln Asn Asp Gly Ile Pro Ser Ser Lys

2740 2745 2750
 Ile Thr Asp Asn Glu Trp Asn Gln Leu Lys Asp Glu Phe Ile Ser Gln
 2755 2760 2765
 Tyr Leu Gln Ser Glu Pro Asn Thr Glu Pro Asn Met Leu Gly Tyr Asn
 2770 2775 2780
 Val Asp Asn Asn Thr His Pro Thr Thr Ser His His Asn Val Glu Glu
 2785 2790 2795 2800
 Lys Pro Phe Ile Met Ser Ile His Asp Arg Asn Leu Phe Ser Gly Glu
 2805 2810 2815
 10 Glu Tyr Asn Tyr Asp Met Phe Asn Ser Gly Asn Asn Pro Ile Asn Ile
 2820 2825 2830
 Ser Asp Ser Thr Asn Ser Met Asp Ser Leu Thr Ser Asn Asn His Ser
 2835 2840 2845
 15 Pro Tyr Asn Asp Lys Asn Asp Leu Tyr Ser Gly Ile Asp Leu Ile Asn
 2850 2855 2860
 Asp Ala Leu Ser Gly Asn His Ile Asp Ile Tyr Asp Glu Met Leu Lys
 2865 2870 2875 2880
 Arg Lys Glu Asn Glu Leu Phe Gly Thr Lys His His Thr Lys His Thr
 2885 2890 2895
 20 Asn Thr Tyr Asn Val Ala Lys Pro Ala Arg Asp Asp Pro Ile Thr Asn
 2900 2905 2910
 Gln Ile Asn Leu Phe His Lys Trp Leu Asp Arg His Arg Asp Met Cys
 2915 2920 2925
 25 Glu Lys Trp Lys Asn Asn His Glu Arg Leu Pro Lys Leu Lys Glu Leu
 2930 2935 2940
 Trp Glu Asn Glu Thr His Ser Gly Asp Ile Asn Ser Gly Ile Pro Ser
 2945 2950 2955 2960
 Gly Asn His Val Leu Asn Thr Asp Val Ser Ile Gln Ile Asp Met Asp
 2965 2970 2975
 30 Asn Pro Lys Thr Lys Asn Glu Ile Thr Asn Met Asp Thr Asn Pro Asp
 2980 2985 2990
 Lys Ser Thr Met Asp Thr Ile Leu Asp Asp Leu Glu Lys Tyr Asn Glu
 2995 3000 3005
 35 Pro Tyr Tyr Tyr Asp Phe Tyr Glu Asp Asp Ile Ile Tyr His Asp Val
 3010 3015 3020
 Asp Val Glu Lys Ser Ser Met Asp Asp Ile Tyr Val Asp His Asn Asn
 3025 3030 3035 3040
 Val Thr Asn Asn Asn Met Asp Val Pro Thr Lys Met His Ile Glu Met
 3045 3050 3055
 40 Asn Ile Val Asn
 3060

(2) INFORMATION FOR SEQ ID NO:15:

45 (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 7295 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

50

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

55 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

TCCAAGCTGT TTTTCTTCT TTTTCTAGTT TTTCCATTGT ATATTCGTCA AATACGTACA 60
 CATATATATA TATATGTATA ACATGTGAGT ATTATTTTAT ACATCACATC GATTACATTT 120
 TAGCGTTTTT TTTCCCCAGA TCACATATAG TACGACTAAG AAACAAAATA ACATCATAAC 180
 60 AAACATAGTG ATTATCAATA CATGATATTA CCACATAATA TAAAGTATTA AATAATATTA 240
 TTGCATGTTA GTGATAACTA CTATATCATA TACACCACTA CTAACATATCA CTACATAGTA 300
 ACAGTAGTAG TCACAATCAT AGCATCATGG TAATATAGAT TTTCAATTCA TATCTTCCTT 360
 ATTGTTTGTT ATACATACAC TATTAATATG TATTTATGTT ATAATGGTAG ACTATGTTAA 420
 CAATGTATGA ATGACCATCA TAAATTAATA ACAGACGCAT CAAAACAGTG TATATGTGTG 480
 65 CATTATATGAC ATAATGTAGT CGGGAAGCAT ACAAATGG AGCCAGGAGG TAGCGGTGGT 540

CGTGGTAGTG GCGGTAGTAG TAGTGGTAAA GGAAGAAGG ATACATCTGA GTATATTTAT 600
GTGAGCGATG CTAAGGATCT TTTGGATAGA GTTGGAGAAA AAGTGTACGA AGAAAAAGTG 660
AAAAATGGTG ATGCTAAAAA ATATATTGAG GCGTTGAAAG GAAATTTGAA CACAGCAAAT 720
GGTCGTAGTT CGGAAACAGC TAGCAGTATT GAAACGTGCA CCCTTGTAAG AGAATATTAT 780
5 GAGCGTGTTA ATGGTGTGG TAAAAGGCAT CCGTGCAGAA AAGACGCAA AAATGAAGAT 840
GTAAACCGTT TTTCCGATAC ACTTGGTGGC CAATGTACAT ACAATAGGAT AAAAGATAGT 900
CAACAGGGTG ATAATAAAGT AGGAGCCTGT GCTCCGTATA GACGATTACA TTTATGTGAT 960
TATAATTTGG AATCTATAGA CACAACGTCG ACGACGCATA AGTTGTTGTT AGAGGTGTGT 1020
ATGGCAGCAA AATACGAAGG AAACCTCAATA AATACACATT ATACACAACA TCAACGAAC 1080
10 AATGAGGATT CTGCTTCCCA ATTATGTACT GTATTAGCAC GAAGTTTTCG AGATATAGGT 1140
GATATCGTAA GAGGAAAAGA TCTATATCTC GGTATGATA ATAAAGAAAA AGAACAAAGA 1200
AAAAAATTAG AACAGAAATT GAAAGATATT TTCAAGAAA TACATAAGGA CGTGATGAAG 1260
ACGAATGGCG CACAAGAACG CTACATAGAT GATGCCAAAG GAGGAGATT TTTTCAATTA 1320
AGAGAAGATT GGTGGACGTC GAATCGAGAA ACAGTATGGA AAGCATTAAAT TTGTCATGCA 1380
15 CCAAAGAAG CTAATTATTT TATAAAAAA GCGTGTAATG TAGGAAAAGG AACTAATGGT 1440
CAATGCCATT GCATTGGTGG AGATGTTCCC ACATATTTTCG ATTATGTGCC GCAGTATCTT 1500
CGCTGGTTTCG AGGAATGGGC AGAAGACTTT TGCAGGAAAA AAAAAAAAAA ACTAGAAAAT 1560
TTGCAAAAAA AGTGTCTGTA TTACGAACAA AATTTATATT GTAGTGGTAA TGGCTACGAT 1620
20 TGCACAAAAA CTATATATAA AAAAGGTAAA CTTGTTATAG GTGAACATTG TACAACTGT 1680
TCTGTTTGGT GTCGTATGTA TGAACTTGG ATAGATAACC AGAAAAAGA ATTTCTAAAA 1740
CAAAAAAGAA AATACGAAAC AGAAATATCA GGTGGTGGTA GTGGTAAGAG TCCTAAAAGG 1800
ACAAAACGGG CTGCACGTAG TAGTAGTATT AGTGTGATA ATGGGTATGA AAGTAAATTT 1860
TATAAAAAA TGAAAGAAGT TGGCTACCA AGTGTGATA AATTTTTTAA AATATTAAAC 1920
AAAGAAGGAA TATGTCAAAA ACAACCTCAA GTAGGAAATG AAAAAAGCAGA TAATGTTGAT 1980
25 TTTACTAATG AAAAATATGT AAAAACATTT TCTCGTACAG AAATTTGTGA ACCGTGCCCA 2040
TGGTGTGGAT TGGAAAAAGG TGGTCCACCA TGGAAAGTTA AAGGTGACAA AACCTGCGGA 2100
AGTGCAAAAA CAAAGACATA CGATCCTAAA AATATTACCG ATATACCAGT ACTCTACCCT 2160
GATAAATCAC AGCAAAATAT ACTAAAAAAT TATAAAAAAT TTTGTGAAAA AGGTGCACCT 2220
GGTGGTGGTC AAATTAATAA ATGGCAATGT TATTATGATG AACATAGGCC TAGTAGTAAA 2280
30 AATAATAATA ATTGTGTAGA AGGAACATGG GACAAGTTTA CACAAGGTAA ACAACCGTT 2340
AAGTCTTATA ATGTTTTTTT TTGGGATTGG GTTCATGATA TGTTACACGA TTCTGTAGAG 2400
TGGAAGACAG AACTTAGTAA GTGTATAAAT AATAACACTA ATGGCAACAC ATGTAGAAAC 2460
AATAATAAAT GTAAAACAGA TTGTGGTTGT TTTCAAAAAT GGGTTGAAAA AAAACAACAA 2520
35 GAATGGATGG CAATAAAAGA CCATTTTGGA AAGCAAACAG ATATTGTCCA AAAAAAGGT 2580
CTTATCGTAT TTAGTCCCTA TGGAGTTCTT GACCTTGT TTGAAGGGCGG TAATCTGTTG 2640
CAAAATATTA AAGATGTTCA TGGAGATACA GATGACATAA AACACATTAA GAACTGTTG 2700
GATGAGGAAG ACGCAGTAGC AGTTGTTCTT GGTGGCAAGG ACAATACCAC AATTGTATAA 2760
TTACTACAAC ACGAAAAAGA ACAAGCAGAA CAATGCAAC AAAAGCAGGA AGAATGCGAG 2820
AAAAAAGCAC AACAAGAAAG TCGTGGTCGC TCCGCCGAAA CCCGCCGAAGA CGAAAGGACA 2880
40 CAACAACCTG CTGATAGTGC CGGCCGAAGT CCGGCCGAAA AAGACGACGA CGACTACGAC 2940
GAAGACGACG AAGATGACGA CGTAGTCCAG GAGGAGGAAG AGGGAAAGGA GGAAGGAACG 3000
GTCACAGAGG TAACAGAGGT AACAGAGGTC GTGGAAGAGA CGGTAACAGA ACAGGAAGGG 3060
GTGAAGCCAT GTGACATAGT GGGCAAACTA TTTGAGGACG ACAAAGTCT CAAAGAGGCA 3120
45 TGTGTTCTAA AATACGGTCC AGGTGGAAAA GAAAAATTC CCAATTGGAA GTGTGTCACA 3180
CCAAGTGGTG TCAGTACTGC CACTAGTGA AAAGACGGCG CTATATGTGT GCCACCCAGG 3240
AGACGACGAT TATACGTAGG TGGTTTATCA CAATGGGCAA GTCGTGGTGG TGACGAGACC 3300
ACGGAGGTGT CGAGTGAAGC CACTTCGGCG CCGTCACAGT CAGAAAGTGA AAAACTACGT 3360
ACTGCGTTTA TTGAGTCCGC TGCAATAGAG ACGTTTTTTT TGTGGCATAA GTATAAGAA 3420
50 GAGAAAAAAC CACCAGCAAC ACAAGATGGA GCGGGACTTG GAGTATCACT CCCAGAACCG 3480
TCACCACCGG GAGAGGACCC CCAAACACAA TTACAACAAA CTGGTGTAT ACCCCCCGAT 3540
TTTTTGCCTC AAATGTTTTA TACATTAGCA GACTACAAAG ACATATTATA CAGTGGTAGT 3600
AACGACACAA GTGACACAAC TGGTAAACAG ACACCTAGTA GTAGTAATGA CAACCTCAA 3660
AATATTGTTT TGGAAGCAAG TGGTAGTACT GAGCAGGAGA AGGAGAAAAA GAAACAAATA 3720
55 CAAGCGAAAA TAAAAAAAT TTTAAACGGT GCCACATCTG GTGTCCCACC TGTCACCAAA 3780
AATAGTGTCA AAACCCCCA ACAACCTGG TGGGAAAAA TCGCGAAGGA TATCTGGAAT 3840
GCTATGGTAT GTGCACTAAC ATATAAGAA AATGACGCCA GAGGCACAAG TGCCAAAATA 3900
GAACAGAATA AGGATTTGAA AAAGGCATT TGGGACGAAG CCAACAAAAA CCCCCCATA 3960
GAGAAATACC AATACACAA TGTCAAACTC GAAGATGAAA GTGGTGCCAA AAGCAACGAC 4020
60 ACCATCCAAC CCCCCACGTT AAAAAATTTT GTGGAATAC CTACATTTT TCGTTGGTTA 4080
CATGAGTGGG GAAACAGTTT TTGTTTTGAG AGAGCAAAAC GATTGGCACA AATAAACAT 4140
GAGTGTATGG ATGAGGATGG TGAAAAACAA TATAGTGGGG ATGGGGAATA TTGTGAAGAA 4200
ATTTTTAGTA AGCAATATAA TGTTCTCCAG GATTTAAGTT CCAGTTGCGC TAAACCTTGT 4260
AGATTGTATA AAACGTGGAT AGAAAAAAA AAACAGAAT ATGAGAAACA ACAAAGGCA 4320
TATGAACAAC AAAAAAGTAA TTACGAAAAT GAACAAAAAG ACAATGCCA AACACAAAGT 4380
65 AATAATAATG CTAATGAATT TTCTAGAACA CTAGGAGCGT CCCCTACAGC TGCAGAATTT 4440

TTACAAAAGT TAGGATCATG TAAAAATGAT AATGGATATG AGAATGGAGA GGATAATAAA 4500
ATAGATTTTA AAAATCCAGA TAAAACATTT AAGGAAGCAC ACAGTTGTGA TCCATGTCCT 4560
ATAACTGGAG TTAATGTCA AAATGGTCAT TGTGTGGGTT CTGCTAATGG AAAGGAGTGC 4620
AAAAACAATA AGATTACTGC AGAAGATATT AAAAATAAGA CAGATCCTAA TGGAAACATA 4680
5 GAAATGGTTG TCAGTGATGA CAGTACAAAT ACATTTGAAC ATTTAGGCGA TTGTAAAAGC 4740
TCAGGTATCT TTAAAGGTAT CAGAAAAGAT GAATGGAAAT GCGCTAATGT ATGTGGTGTA 4800
GATATATGTA CTCTGGAAAA AAAAATTAAG AATGGGCAAG AAGGTGATAA AAAATATATC 4860
ACAATGAAAG AATTGCTTAA ACGATGGCTA GAATATTTT TAGAAGATTA TAATAGAATT 4920
AGAAAAAATA TAAAGCTATG TACGAAAAAG GAAGATGGAT GCAAATGTAT AAAAGGTTGT 4980
10 ATAGAAAAAT GGGTACAAGA AAAAACGAAA GAATGGCAAA AAATAAACGA TACTTATCTT 5040
GAACAATATA AAAATGATGA TGGTAATACT TTAATAATT TTTTGGAGCA ATTCCAATAT 5100
CGAACTGAAT TTAAAAACGC TATAAAACCT TGTGATGGTT TAGACCAGTT CAAGACTTCG 5160
TGTGGTCTTA ATAGTACTGA TAATTCACAA AATGGTAATA ATAACGATCT TGTCTATGT 5220
TTGCTTAATA AACTTCAAAA AAAAATTAGT GAGTGTAAG AACACATAG TGGCCAAACC 5280
15 CAAACACCGT GTGATAACTC TTCCCTTAGT GGTAAAGAAT CCACCCTCGT TGAAGACGTT 5340
GATGATTATG AGGAACAAAA CCCAGAAAAC AAAGTGGAAAC AACCTAAATT TTGTCCAGAT 5400
ATGAAAGAAC CAAAAAAGA AAACGATGAA GAAGTAGGCA CTTGTGGCGG AGACGAAGAA 5460
AAAAAAAAG TGAAGACAG TGTAAATCGAA CAAAAGAGG AAGAAGCAGC TAGTGCCCCA 5520
GAGGAATCTC CTCCATTAAC CCCGGAAGCA CCAAAAAAAG AGGAAAATGT GGTACCAAAA 5580
20 CCACCACCAC CACCAAAAAA ACGCCGAATC AAAACCCGTA ATGTGTTGGA CCACCCCGCT 5640
GTCTAGCCCG CCTCATGTC TTCTACCATC ATGTGGAGTA TTGGCATCGG TTTTGCTGCG 5700
TTCACCTATT TTTATCTAAA GAAAAAAGC AAATCATCTG TTGGAATTTT ATTCCAAATA 5760
CTGCAAATAC CCAAAGTGA TTATGATATA CCTACATTGA AATCAAGCAA TCGTTATATA 5820
CCCTATGCAA GTGATAGACA TAAAGGCAAA ACATATATTT ATATGGAAGG AGATAGCAGT 5880
25 GGAGATGAAA AATATGCATT TATGTCTGAT ACTACTGATA TAACTTCATC CGAAAGTGAG 5940
TATGAAGAAT TGGATATTAA TGATATATAT GTACCAGGTA GTCCTAAATA TAAAACATTG 6000
ATAGAAGTAG TACTTGAACC ATCAAAAAGA GATACACAAA ATGATATACA CAATGATATA 6060
CCTAGTGATA TACCAAATAG TGACACACCA CCACCCATTA CTGATGATGA AATGGAATCAA 6120
TTGAAAAAAG ATTTTATATC TAATATGTTA CAAAATACAC AAAATACGGA ACCAAATATT 6180
30 TTACATGATA ATGTGGATAA TAATACCCAT CCTACCATGT CACGTCATAA TATGGACCAA 6240
AAACCTTTTA TTATGTCCAT ACATGATAGA AATTTATTTA GTGGAGAAGA ATACAATTAT 6300
GATATGTTTA ATAGTGGGAA TAATCCAATA AACATTAGTG ATTCACAAA TAGTATGGAT 6360
AGTCTAATCA GTAACAACCA TAGTCCATAT AATGATAAAA ATGATTTATA TAGTGGTATC 6420
GACCTAATCA ACGACGACT AAGTGGTAAT CATATTGATA TATATGATGA AATGCTCAA 6480
35 CGAAAAAGAA ATGAATTATT CGGGACGCAA CATCATCAA AAAATATAAC GTCTAACCGT 6540
GTCGTTACCC AAACAAGTAG TGACGACCCT ATAACCAATC AAATAAATTT GTTCCATAAA 6600
TGGTTAGATA GGCATAGAGA TATGTGCGAA AAGTGGAAAA ATAATCACGA ACGGTTACCC 6660
AAATTGAAAG AATTGTGGGA AAATGAGACA CATAGTGGTG ACATAAATAG TGGTATACCT 6720
AGTGGTAACC ATGTGTTGAA TACTGATGTT TCTATTCAA TAGATATGGA TAATCCGAAA 6780
40 ACAATGAATG AATTTACTAA TATGGATACA AACCCTGACA AATCTACTAT GGATACTATA 6840
TTGGATGATC TAGAAAAATA TAACGAACCC TACTACTATG ATTTTATATA ACATGATATC 6900
TATTATGATG TAAATGATGA TAAAGCATCT GAGGATCATA TAAATATGGA TCATAATAAG 6960
ATGGATAATA ATAATTCGGA TGTCCCCACT AACGTACAAA TTGAAATGAA TGTCATTAAT 7020
AATCAGGAGT TACTACAAA TGAATATCCT ATATCGCATA TGTAGGGAAT ATGAAAATAA 7080
45 TAGATGTATA TATGTTTTTT TCTTTTTTTG TGTGTGTGCA GTTTATATTT TTTATTTGTA 7140
GATGTTATAT ATTTTTTTT TTTGTGGGTT ATATTATAAT TTTTATTTAT GGGTTATATA 7200
TATATTTTTT TTTTGTGCA TTTGTCTATT TTTTATTTGT GCTTTATATA TATATATATT 7260
TTATTCAGCT TGGACTTAAC CAGGCTGAAC TTGCT 7295

50 (2) INFORMATION FOR SEQ ID NO:16:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2182 amino acids
(B) TYPE: amino acid
55 (C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

60 (iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

65 (v) FRAGMENT TYPE: N-terminal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

	Met	Glu	Pro	Gly	Gly	Ser	Gly	Gly	Arg	Gly	Ser	Gly	Gly	Ser	Ser	Ser
5	1				5				10					15		
	Gly	Lys	Gly	Lys	Lys	Asp	Thr	Ser	Glu	Tyr	Ile	Tyr	Val	Ser	Asp	Ala
			20						25					30		
	Lys	Asp	Leu	Leu	Asp	Arg	Val	Gly	Glu	Lys	Val	Tyr	Glu	Glu	Lys	Val
		35						40					45			
10	Lys	Asn	Gly	Asp	Ala	Lys	Lys	Tyr	Ile	Glu	Ala	Leu	Lys	Gly	Asn	Leu
		50					55					60				
	Asn	Thr	Ala	Asn	Gly	Arg	Ser	Ser	Glu	Thr	Ala	Ser	Ser	Ile	Glu	Thr
	65					70					75				80	
	Cys	Thr	Leu	Val	Lys	Glu	Tyr	Tyr	Glu	Arg	Val	Asn	Gly	Asp	Gly	Lys
				85					90					95		
15	Arg	His	Pro	Cys	Arg	Lys	Asp	Ala	Lys	Asn	Glu	Asp	Val	Asn	Arg	Phe
			100						105					110		
	Ser	Asp	Thr	Leu	Gly	Gly	Gln	Cys	Thr	Tyr	Asn	Arg	Ile	Lys	Asp	Ser
		115					120						125			
20	Gln	Gln	Gly	Asp	Asn	Lys	Val	Gly	Ala	Cys	Ala	Pro	Tyr	Arg	Arg	Leu
		130					135					140				
	His	Leu	Cys	Asp	Tyr	Asn	Leu	Glu	Ser	Ile	Asp	Thr	Thr	Ser	Thr	Thr
	145					150					155				160	
	His	Lys	Leu	Leu	Leu	Glu	Val	Cys	Met	Ala	Ala	Lys	Tyr	Glu	Gly	Asn
				165					170					175		
25	Ser	Ile	Asn	Thr	His	Tyr	Thr	Gln	His	Gln	Arg	Thr	Asn	Glu	Asp	Ser
			180					185					190			
	Ala	Ser	Gln	Leu	Cys	Thr	Val	Leu	Ala	Arg	Ser	Phe	Ala	Asp	Ile	Gly
		195						200					205			
30	Asp	Ile	Val	Arg	Gly	Lys	Asp	Leu	Tyr	Leu	Gly	Tyr	Asp	Asn	Lys	Glu
		210					215					220				
	Lys	Glu	Gln	Arg	Lys	Lys	Leu	Glu	Gln	Lys	Leu	Lys	Asp	Ile	Phe	Lys
	225					230					235				240	
	Lys	Ile	His	Lys	Asp	Val	Met	Lys	Thr	Asn	Gly	Ala	Gln	Glu	Arg	Tyr
				245						250					255	
35	Ile	Asp	Asp	Ala	Lys	Gly	Gly	Asp	Phe	Phe	Gln	Leu	Arg	Glu	Asp	Trp
			260					265					270			
	Trp	Thr	Ser	Asn	Arg	Glu	Thr	Val	Trp	Lys	Ala	Leu	Ile	Cys	His	Ala
		275						280					285			
40	Pro	Lys	Glu	Ala	Asn	Tyr	Phe	Ile	Lys	Thr	Ala	Cys	Asn	Val	Gly	Lys
		290					295					300				
	Gly	Thr	Asn	Gly	Gln	Cys	His	Cys	Ile	Gly	Gly	Asp	Val	Pro	Thr	Tyr
	305				310					315					320	
	Phe	Asp	Tyr	Val	Pro	Gln	Tyr	Leu	Arg	Trp	Phe	Glu	Glu	Trp	Ala	Glu
				325						330					335	
45	Asp	Phe	Cys	Arg	Lys	Lys	Lys	Lys	Lys	Leu	Glu	Asn	Leu	Gln	Lys	Gln
			340						345				350			
	Cys	Arg	Asp	Tyr	Glu	Gln	Asn	Leu	Tyr	Cys	Ser	Gly	Asn	Gly	Tyr	Asp
		355					360					365				
50	Cys	Thr	Lys	Thr	Ile	Tyr	Lys	Lys	Gly	Lys	Leu	Val	Ile	Gly	Glu	His
		370					375					380				
	Cys	Thr	Asn	Cys	Ser	Val	Trp	Cys	Arg	Met	Tyr	Glu	Thr	Trp	Ile	Asp
	385					390					395				400	
	Asn	Gln	Lys	Lys	Glu	Phe	Leu	Lys	Gln	Lys	Arg	Lys	Tyr	Glu	Thr	Glu
				405						410					415	
55	Ile	Ser	Gly	Gly	Gly	Ser	Gly	Lys	Ser	Pro	Lys	Arg	Thr	Lys	Arg	Ala
			420						425					430		
	Ala	Arg	Ser	Ser	Ser	Ser	Ser	Asp	Asn	Gly	Tyr	Glu	Ser	Lys	Phe	
		435						440					445			
60	Tyr	Lys	Lys	Leu	Lys	Glu	Val	Gly	Tyr	Gln	Asp	Val	Asp	Lys	Phe	Leu
		450					455					460				
	Lys	Ile	Leu	Asn	Lys	Glu	Gly	Ile	Cys	Gln	Lys	Gln	Pro	Gln	Val	Gly
	465					470					475				480	
	Asn	Glu	Lys	Ala	Asp	Asn	Val	Asp	Phe	Thr	Asn	Glu	Lys	Tyr	Val	Lys
				485						490				495		
65	Thr	Phe	Ser	Arg	Thr	Glu	Ile	Cys	Glu	Pro	Cys	Pro	Trp	Cys	Gly	Leu

				500				505				510				
	Glu	Lys	Gly	Gly	Pro	Pro	Trp	Lys	Val	Lys	Gly	Asp	Lys	Thr	Cys	Gly
			515					520					525			
5	Ser	Ala	Lys	Thr	Lys	Thr	Tyr	Asp	Pro	Lys	Asn	Ile	Thr	Asp	Ile	Pro
		530					535					540				
	Val	Leu	Tyr	Pro	Asp	Lys	Ser	Gln	Gln	Asn	Ile	Leu	Lys	Lys	Tyr	Lys
	545					550					555					560
	Asn	Phe	Cys	Glu	Lys	Gly	Ala	Pro	Gly	Gly	Gly	Gln	Ile	Lys	Lys	Trp
				565							570					575
10	Gln	Cys	Tyr	Tyr	Asp	Glu	His	Arg	Pro	Ser	Ser	Lys	Asn	Asn	Asn	Asn
				580					585					590		
	Cys	Val	Glu	Gly	Thr	Trp	Asp	Lys	Phe	Thr	Gln	Gly	Lys	Gln	Thr	Val
			595					600					605			
15	Lys	Ser	Tyr	Asn	Val	Phe	Phe	Trp	Asp	Trp	Val	His	Asp	Met	Leu	His
		610					615					620				
	Asp	Ser	Val	Glu	Trp	Lys	Thr	Glu	Leu	Ser	Lys	Cys	Ile	Asn	Asn	Asn
	625					630					635					640
	Thr	Asn	Gly	Asn	Thr	Cys	Arg	Asn	Asn	Asn	Lys	Cys	Lys	Thr	Asp	Cys
				645							650					655
20	Gly	Cys	Phe	Gln	Lys	Trp	Val	Glu	Lys	Lys	Gln	Gln	Glu	Trp	Met	Ala
				660					665						670	
	Ile	Lys	Asp	His	Phe	Gly	Lys	Gln	Thr	Asp	Ile	Val	Gln	Gln	Lys	Gly
			675				680					685				
25	Leu	Ile	Val	Phe	Ser	Pro	Tyr	Gly	Val	Leu	Asp	Leu	Val	Leu	Lys	Gly
		690					695					700				
	Gly	Asn	Leu	Leu	Gln	Asn	Ile	Lys	Asp	Val	His	Gly	Asp	Thr	Asp	Asp
	705					710					715					720
	Ile	Lys	His	Ile	Lys	Lys	Leu	Leu	Asp	Glu	Glu	Asp	Ala	Val	Ala	Val
				725						730					735	
30	Val	Leu	Gly	Gly	Lys	Asp	Asn	Thr	Thr	Ile	Asp	Lys	Leu	Leu	Gln	His
				740					745					750		
	Glu	Lys	Glu	Gln	Ala	Glu	Gln	Cys	Lys	Gln	Lys	Gln	Glu	Glu	Cys	Glu
			755					760					765			
35	Lys	Lys	Ala	Gln	Gln	Glu	Ser	Arg	Gly	Arg	Ser	Ala	Glu	Thr	Arg	Glu
			770				775					780				
	Asp	Glu	Arg	Thr	Gln	Gln	Pro	Ala	Asp	Ser	Ala	Gly	Glu	Val	Glu	Glu
	785					790					795					800
	Glu	Glu	Asp	Asp	Asp	Asp	Tyr	Asp	Glu	Asp	Asp	Glu	Asp	Asp	Asp	Val
				805						810					815	
40	Val	Gln	Glu	Glu	Glu	Gly	Lys	Glu	Glu	Gly	Thr	Val	Thr	Thr	Glu	Val
				820					825					830		
	Thr	Glu	Val	Thr	Glu	Val	Val	Glu	Glu	Thr	Val	Thr	Glu	Gln	Glu	Gly
			835					840					845			
45	Val	Lys	Pro	Cys	Asp	Ile	Val	Gly	Lys	Leu	Phe	Glu	Asp	Asp	Lys	Ser
		850					855					860				
	Leu	Lys	Glu	Ala	Cys	Gly	Leu	Lys	Tyr	Gly	Pro	Gly	Gly	Lys	Glu	Lys
	865					870					875					880
	Phe	Pro	Asn	Trp	Lys	Cys	Val	Thr	Pro	Ser	Gly	Val	Ser	Thr	Ala	Thr
				885						890					895	
50	Ser	Gly	Lys	Asp	Gly	Ala	Ile	Cys	Val	Pro	Pro	Arg	Arg	Arg	Arg	Leu
				900					905					910		
	Tyr	Val	Gly	Gly	Leu	Ser	Gln	Trp	Ala	Ser	Arg	Gly	Gly	Asp	Glu	Thr
			915					920					925			
55	Thr	Glu	Val	Ser	Ser	Glu	Ala	Thr	Ser	Ala	Pro	Ser	Gln	Ser	Glu	Ser
			930				935					940				
	Glu	Lys	Leu	Arg	Thr	Ala	Phe	Ile	Glu	Ser	Ala	Ala	Ile	Glu	Thr	Phe
	945					950					955					960
	Phe	Leu	Trp	His	Lys	Tyr	Lys	Glu	Glu	Lys	Lys	Pro	Pro	Ala	Thr	Gln
				965						970					975	
60	Asp	Gly	Ala	Gly	Leu	Gly	Val	Ser	Leu	Pro	Glu	Pro	Ser	Pro	Pro	Gly
				980					985					990		
	Glu	Asp	Pro	Gln	Thr	Gln	Leu	Gln	Gln	Thr	Gly	Val	Ile	Pro	Pro	Asp
			995					1000					1005			
65	Phe	Leu	Arg	Gln	Met	Phe	Tyr	Thr	Leu	Ala	Asp	Tyr	Lys	Asp	Ile	Leu
		1010					1015						1020			

Tyr Ser Gly Ser Asn Asp Thr Ser Asp Thr Thr Gly Lys Gln Thr Pro
 1025 1030 1035 1040
 Ser Ser Ser Asn Asp Asn Leu Lys Asn Ile Val L u Glu Ala Ser Gly
 1045 1050 1055
 5 Ser Thr Glu Gln Glu Lys Glu Lys Met Lys Gln Ile Gln Ala Lys Ile
 1060 1065 1070
 Lys Lys Ile Leu Asn Gly Ala Thr Ser Gly Val Pro Pro Val Thr Lys
 1075 1080 1085
 10 Asn Ser Val Lys Thr Pro Gln Gln Thr Trp Trp Glu Asn Ile Ala Lys
 1090 1095 1100
 Asp Ile Trp Asn Ala Met Val Cys Ala Leu Thr Tyr Lys Glu Asn Asp
 1105 1110 1115 1120
 Ala Arg Gly Thr Ser Ala Lys Ile Glu Gln Asn Lys Asp Leu Lys Lys
 1125 1130 1135
 15 Ala Leu Trp Asp Glu Ala Asn Lys Asn Thr Pro Ile Glu Lys Tyr Gln
 1140 1145 1150
 Tyr Thr Asn Val Lys Leu Glu Asp Glu Ser Gly Ala Lys Ser Asn Asp
 1155 1160 1165
 20 Thr Ile Gln Pro Pro Thr Leu Lys Asn Phe Val Glu Ile Pro Thr Phe
 1170 1175 1180
 Phe Arg Trp Leu His Glu Trp Gly Asn Ser Phe Cys Phe Glu Arg Ala
 1185 1190 1195 1200
 Lys Arg Leu Ala Gln Ile Lys His Glu Cys Met Asp Glu Asp Gly Glu
 1205 1210 1215
 25 Lys Gln Tyr Ser Gly Asp Gly Glu Tyr Cys Glu Glu Ile Phe Ser Lys
 1220 1225 1230
 Gln Tyr Asn Val Leu Gln Asp Leu Ser Ser Ser Cys Ala Lys Pro Cys
 1235 1240 1245
 30 Arg Leu Tyr Lys Thr Trp Ile Glu Lys Lys Lys Thr Glu Tyr Glu Lys
 1250 1255 1260
 Gln Gln Lys Ala Tyr Glu Gln Gln Lys Ser Asn Tyr Glu Asn Glu Gln
 1265 1270 1275 1280
 Lys Asp Lys Cys Gln Thr Gln Ser Asn Asn Asn Ala Asn Glu Phe Ser
 1285 1290 1295
 35 Arg Thr Leu Gly Ala Ser Pro Thr Ala Ala Glu Phe Leu Gln Lys Leu
 1300 1305 1310
 Gly Ser Cys Lys Asn Asp Asn Gly Tyr Glu Asn Gly Glu Asp Asn Lys
 1315 1320 1325
 40 Ile Asp Phe Lys Asn Pro Asp Lys Thr Phe Lys Glu Ala His Ser Cys
 1330 1335 1340
 Asp Pro Cys Pro Ile Thr Gly Val Lys Cys Gln Asn Gly His Cys Val
 1345 1350 1355 1360
 Gly Ser Ala Asn Gly Lys Glu Cys Lys Asn Asn Lys Ile Thr Ala Glu
 1365 1370 1375
 45 Asp Ile Lys Asn Lys Thr Asp Pro Asn Gly Asn Ile Glu Met Val Val
 1380 1385 1390
 Ser Asp Asp Ser Thr Asn Thr Phe Glu His Leu Gly Asp Cys Lys Ser
 1395 1400 1405
 50 Ser Gly Ile Phe Lys Gly Ile Arg Lys Asp Glu Trp Lys Cys Ala Asn
 1410 1415 1420
 Val Cys Gly Val Asp Ile Cys Thr Leu Glu Lys Lys Ile Lys Asn Gly
 1425 1430 1435 1440
 Gln Glu Gly Asp Lys Lys Tyr Ile Thr Met Lys Glu Leu Leu Lys Arg
 1445 1450 1455
 55 Trp Leu Glu Tyr Phe Leu Glu Asp Tyr Asn Arg Ile Arg Lys Lys Ile
 1460 1465 1470
 Lys Leu Cys Thr Lys Lys Glu Asp Gly Cys Lys Cys Ile Lys Gly Cys
 1475 1480 1485
 60 Ile Glu Lys Trp Val Gln Glu Lys Thr Lys Glu Trp Gln Lys Ile Asn
 1490 1495 1500
 Asp Thr Tyr Leu Glu Gln Tyr Lys Asn Asp Asp Gly Asn Thr Leu Thr
 1505 1510 1515 1520
 Asn Phe Leu Glu Gln Phe Gln Tyr Arg Thr Glu Phe Lys Asn Ala Ile
 1525 1530 1535
 65 Lys Pro Cys Asp Gly Leu Asp Gln Phe Lys Thr Ser Cys Gly Leu Asn

					1540					1545					1550				
	Ser Thr Asp Asn Ser Gln Asn Gly Asn Asn Asn Asp Leu Val Leu Cys																		
		1555					1560								1565				
5	Leu Leu Asn Lys Leu Gln Lys Lys Ile Ser Glu Cys Lys Glu Gln His					1570	1575							1580					
	Ser Gly Gln Thr Gln Thr Pro Cys Asp Asn Ser Ser Leu Ser Gly Lys					1590							1595						1600
	Glu Ser Thr Leu Val Glu Asp Val Asp Asp Tyr Glu Glu Gln Asn Pro				1605						1610								1615
10	Glu Asn Lys Val Glu Gln Pro Lys Phe Cys Pro Asp Met Lys Glu Pro				1620					1625									1630
	Lys Lys Glu Asn Asp Glu Glu Val Gly Thr Cys Gly Gly Asp Glu Glu				1635					1640									1645
15	Lys Lys Lys Val Glu Asp Ser Val Ile Glu Gln Lys Glu Glu Glu Ala				1650					1655									1660
	Ala Ser Ala Pro Glu Glu Ser Pro Pro Leu Thr Pro Glu Ala Pro Lys				1665					1670									1675
	Lys Glu Glu Asn Val Pro Lys Pro Pro Pro Pro Lys Lys Arg				1685					1690									1695
20	Arg Ile Lys Thr Arg Asn Val Leu Asp His Pro Ala Val Ile Pro Ala				1700					1705									1710
	Leu Met Ser Ser Thr Ile Met Trp Ser Ile Gly Ile Gly Phe Ala Ala				1715					1720									1725
25	Phe Thr Tyr Phe Tyr Leu Lys Lys Lys Thr Lys Ser Ser Val Gly Asn				1730					1735									1740
	Leu Phe Gln Ile Leu Gln Ile Pro Lys Ser Asp Tyr Asp Ile Pro Thr				1745					1750									1755
	Leu Lys Ser Ser Asn Arg Tyr Ile Pro Tyr Ala Ser Asp Arg His Lys				1765					1770									1775
30	Gly Lys Thr Tyr Ile Tyr Met Glu Gly Asp Ser Ser Gly Asp Glu Lys				1780					1785									1790
	Tyr Ala Phe Met Ser Asp Thr Thr Asp Ile Thr Ser Ser Glu Ser Glu				1795					1800									1805
35	Tyr Glu Glu Leu Asp Ile Asn Asp Ile Tyr Val Pro Gly Ser Pro Lys				1810					1815									1820
	Tyr Lys Thr Leu Ile Glu Val Val Leu Glu Pro Ser Lys Arg Asp Thr				1825					1830									1835
	Gln Asn Asp Ile His Asn Asp Ile Pro Ser Asp Ile Pro Asn Ser Asp				1845					1850									1855
40	Thr Pro Pro Pro Ile Thr Asp Asp Glu Trp Asn Gln Leu Lys Lys Asp				1860					1865									1870
	Phe Ile Ser Asn Met Leu Gln Asn Thr Gln Asn Thr Glu Pro Asn Ile				1875					1880									1885
45	Leu His Asp Asn Val Asp Asn Asn Thr His Pro Thr Met Ser Arg His				1890					1895									1900
	Asn Met Asp Gln Lys Pro Phe Ile Met Ser Ile His Asp Arg Asn Leu				1905					1910									1915
	Phe Ser Gly Glu Glu Tyr Asn Tyr Asp Met Phe Asn Ser Gly Asn Asn				1925					1930									1935
50	Pro Ile Asn Ile Ser Asp Ser Thr Asn Ser Met Asp Ser Leu Thr Ser				1940					1945									1950
	Asn Asn His Ser Pro Tyr Asn Asp Lys Asn Asp Leu Tyr Ser Gly Ile				1955					1960									1965
	Asp Leu Ile Asn Asp Ala Leu Ser Gly Asn His Ile Asp Ile Tyr Asp				1970					1975									1980
55	Glu Met Leu Lys Arg Lys Glu Asn Glu Leu Phe Gly Thr Gln His His				1985					1990									1995
	Pro Lys Asn Ile Thr Ser Asn Arg Val Val Thr Gln Thr Ser Ser Asp				2005					2010									2015
60	Asp Pro Ile Thr Asn Gln Ile Asn Leu Phe His Lys Trp Leu Asp Arg				2020					2025									2030
	His Arg Asp Met Cys Glu Lys Trp Lys Asn Asn His Glu Arg Leu Pro				2035					2040									2045
	Lys Leu Lys Glu Leu Trp Glu Asn Glu Thr His Ser Gly Asp Ile Asn				2050					2055									

Ser Gly Ile Pro Ser Gly Asn His Val Leu Asn Thr Asp Val Ser Ile
 2065 2070 2075 2080
 Gln Ile Asp Met Asp Asn Pro Lys Thr Met Asn Glu Phe Thr Asn Met
 2085 2090 2095
 5 Asp Thr Asn Pro Asp Lys Ser Thr Met Asp Thr Ile Leu Asp Asp Leu
 2100 2105 2110
 Glu Lys Tyr Asn Glu Pro Tyr Tyr Tyr Asp Phe Tyr Lys His Asp Ile
 2115 2120 2125
 10 Tyr Tyr Asp Val Asn Asp Asp Lys Ala Ser Glu Asp His Ile Asn Met
 2130 2135 2140
 Asp His Asn Lys Met Asp Asn Asn Asn Ser Asp Val Pro Thr Asn Val
 2145 2150 2155 2160
 Gln Ile Glu Met Asn Val Ile Asn Asn Gln Glu Leu Leu Gln Asn Glu
 2165 2170 2175
 15 Tyr Pro Ile Ser His Met
 2180

(2) INFORMATION FOR SEQ ID NO:17:

- 20 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 30 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 25 (ii) MOLECULE TYPE: cDNA
 (iii) HYPOTHETICAL: NO
 (iv) ANTISENSE: NO
 (v) FRAGMENT TYPE:
 30 (vi) ORIGINAL SOURCE:
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

ATCGATCAGC TGGGAAGAAA TACTTCATCT

30

(2) INFORMATION FOR SEQ ID NO:18:

- 40 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 30 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 45 (ii) MOLECULE TYPE: cDNA
 (iii) HYPOTHETICAL: NO
 (iv) ANTISENSE: NO
 (v) FRAGMENT TYPE:
 (vi) ORIGINAL SOURCE:
 50 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

ATCGATGGGC CCCGAAGTTT GTTCATTATT

30

(2) INFORMATION FOR SEQ ID NO:19:

- 55 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 30 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 60 (D) TOPOLOGY: linear
 (ii) MOLECULE TYPE: cDNA
 (iii) HYPOTHETICAL: NO
 (iv) ANTISENSE: NO
 65 (v) FRAGMENT TYPE:

(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

5 TCTCGTCAGC TGACGATCTC TAGTGCTATT

30

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(v) FRAGMENT TYPE:

(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

ACGAGTGGGC CCTGTCACAA CTCCTGAGT

30

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 17 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(v) FRAGMENT TYPE:

(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

AGACCTCAAT TTCTAAG

17

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 18 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(v) FRAGMENT TYPE:

(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

AATCGCGAGC ATCATCTG

18

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
- (B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

CCRAGRAGRC AARAAATATG

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

CCAWCKKARR AATTGWGG

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 291 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE: internal
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

Cys	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Cys	Xaa	Xaa
1				5				10					15		
Xaa	Xaa	Xaa	Val	Cys	Ile	Pro	Asp	Arg	Arg	Tyr	Gln	Leu	Cys	Met	Lys
			20					25					30		
Glu	Leu	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
		35					40					45			
Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
		50				55					60				
Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
		65				70					75				80
Xaa	Asp	Phe	Cys	Lys	Asp	Ile	Arg	Trp	Ser	Leu	Gly	Asp	Phe	Gly	Asp
			85					90					95		
Ile	Ile	Met	Gly	Thr	Asp	Met	Glu	Gly	Ile	Gly	Tyr	Ser	Lys	Xaa	Xaa
			100					105					110		
Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Thr	Asp	Glu	Lys	Ala	Gln	Gln
		115				120					125				
Arg	Arg	Lys	Gln	Trp	Trp	Asn	Glu	Ser	Lys	Ala	Gln	Ile	Trp	Thr	Ala
		130				135					140				

	Met	Met	Tyr	Ser	Val	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
	145					150					155					160
	Cys	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Glu	Pro	Gln	Ile	Tyr	Arg	Trp	
					165				170						175	
5	Ile	Arg	Glu	Trp	Gly	Arg	Asp	Tyr	Val	Ser	Glu	Leu	Pro	Thr	Glu	Val
				180				185						190		
	Gln	Lys	Leu	Lys	Glu	Lys	Cys	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
			195					200						205		
	Xaa	Xaa	Cys	Xaa	Val	Pro	Pro	Cys	Gln	Asn	Ala	Cys	Lys	Ser	Tyr	Asp
10		210					215					220				
	Gln	Trp	Ile	Thr	Arg	Lys	Lys	Asn	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
	225					230					235					240
	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
					245					250					255	
15	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
				260				265						270		
	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
			275				280						285			
	Cys	Xaa	Cys													
20		290														

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 271 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
 (iii) HYPOTHETICAL: NO
 (iv) ANTISENSE: NO
 (v) FRAGMENT TYPE: internal
 (vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

	Cys	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Cys	Xaa	Xaa	Xaa	Xaa	Xaa
	1				5				10					15		
40	Xaa	Xaa	Xaa	Xaa	Val	Cys	Ile	Pro	Asp	Arg	Arg	Ile	Gln	Leu	Cys	
				20				25					30			
	Ile	Val	Asn	Leu	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
			35					40					45			
45	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
		50				55					60					
	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Lys	Phe	Cys	Asn	Asp	Leu	Lys	Asn	
	65				70				75					80		
	Ser	Phe	Leu	Asp	Tyr	Gly	His	Leu	Ala	Met	Gly	Asn	Asp	Met	Asp	Phe
				85					90					95		
50	Gly	Gly	Tyr	Ser	Thr	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
				100				105						110		
	Xaa	Xaa	Xaa	Xaa	Xaa	Ser	Glu	His	Lys	Ile	Lys	Asn	Phe	Arg	Lys	
			115				120					125				
55	Glu	Trp	Trp	Asn	Glu	Phe	Arg	Glu	Lys	Leu	Trp	Glu	Ala	Met	Leu	Ser
		130					135					140				
	Glu	His	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Cys	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Glu
	145				150				155						160	
	Leu	Gln	Ile	Thr	Gln	Trp	Ile	Lys	Glu	Trp	His	Gly	Glu	Phe	Leu	Leu
				165					170						175	
60	Glu	Arg	Asp	Asn	Arg	Ser	Lys	Leu	Pro	Lys	Ser	Lys	Cys	Xaa	Xaa	Xaa
				180					185					190		
	Xaa	Xaa	Xaa	Xaa	Xaa	Cys	Xaa	Glu	Lys	Glu	Cys	Ile	Asp	Pro	Cys	Met
			195				200					205				
	Lys	Tyr	Arg	Asp	Trp	Ile	Ile	Arg	Ser	Lys	Phe	Xaa	Xaa	Xaa	Xaa	Xaa
65		210					215					220				

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 225 230 235 240
 Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 245 250 255
 5 Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Cys
 260 265 270

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 277 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa
 1 5 10 15
 Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Val Cys Val Pro Pro Arg Arg
 20 25 30
 Gln Glu Leu Cys Leu Gly Asn Ile Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 35 40 45
 Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 50 55 60
 Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Glu Val Cys Lys
 65 70 75 80
 Ile Ile Asn Lys Thr Phe Ala Asp Ile Arg Asp Ile Ile Gly Gly Thr
 85 90 95
 Asp Tyr Trp Asn Asp Leu Ser Asn Arg Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 100 105 110
 Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asn Lys Lys Asn Asp Lys Leu Phe
 115 120 125
 Arg Asp Glu Trp Trp Lys Val Ile Lys Lys Asp Val Trp Asn Val Ile
 130 135 140
 Ser Trp Phe Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 145 150 155 160
 Ile Pro Gln Phe Phe Arg Trp Phe Ser Glu Trp Gly Asp Asp Tyr Cys
 165 170 175
 Gln Asp Lys Thr Lys Met Ile Glu Thr Leu Lys Val Glu Cys Xaa Xaa
 180 185 190
 Xaa Xaa Cys Xaa Asp Asp Asn Cys Lys Ser Lys Cys Asn Ser Tyr Lys
 195 200 205
 Glu Trp Ile Ser Lys Lys Lys Lys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 210 215 220
 Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 225 230 235 240
 Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa
 245 250 255
 Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 260 265 270
 Xaa Cys Xaa Xaa Cys
 275

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 282 amino acids
 (B) TYPE: amino acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

5 (ii) MOLECULE TYPE: peptide
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE: internal
(vi) ORIGINAL SOURCE:

10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

	Cys	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Cys	Xaa	Xaa
	1				5					10				15		
15	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Val	Cys	Gly	Pro	Pro	Arg	Arg	
				20					25					30		
	Gln	Gln	Leu	Cys	Leu	Gly	Tyr	Ile	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
			35					40					45			
	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
			50				55					60				
20	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Lys	Ile	Cys	Asn	
	65				70					75				80		
	Ala	Ile	Leu	Gly	Ser	Tyr	Ala	Asp	Ile	Gly	Asp	Ile	Val	Arg	Gly	Leu
				85					90					95		
25	Asp	Val	Trp	Arg	Asp	Ile	Asn	Thr	Asn	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
				100				105						110		
	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Lys	Lys	Gln	Asn	Asp	Asn
			115				120						125			
	Asn	Glu	Arg	Asn	Lys	Trp	Trp	Glu	Lys	Gln	Arg	Asn	Leu	Ile	Trp	Ser
	130					135						140				
30	Ser	Met	Val	Lys	His	Ile	Xaa	Xaa	Xaa	Xaa	Xaa	Cys	Xaa	Xaa	Xaa	Xaa
	145				150					155				160		
	Xaa	Xaa	Xaa	Xaa	Ile	Pro	Gln	Phe	Leu	Arg	Trp	Leu	Lys	Glu	Trp	Gly
				165				170						175		
35	Asp	Glu	Phe	Cys	Glu	Glu	Met	Gly	Thr	Glu	Val	Lys	Gln	Leu	Glu	Lys
			180					185						190		
	Ile	Cys	Xaa	Xaa	Xaa	Xaa	Cys	Xaa	Glu	Lys	Lys	Cys	Lys	Asn	Ala	Cys
			195				200						205			
	Ser	Ser	Tyr	Glu	Lys	Trp	Ile	Lys	Glu	Arg	Lys	Asn	Xaa	Xaa	Xaa	Xaa
	210					215						220				
40	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
	225				230					235				240		
	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
				245				250						255		
45	Xaa	Xaa	Cys	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
			260				265						270			
	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Cys	Xaa	Xaa	Cys						
			275				280									

(2) INFORMATION FOR SEQ ID NO:29:

50 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 324 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
55 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
60 (v) FRAGMENT TYPE: internal
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

65 Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa

[illegible]

(2) INFORMATION FOR SEQ ID NO:30:

45. (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 362 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

50 (ii) MOLECULE TYPE: peptide
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
55 (v) FRAGMENT TYPE: internal
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

	Ala	Cys	Ala	Pro	Tyr	Arg	Arg	Leu	His	Leu	Cys	Asp	Tyr	Asn	Leu	Xaa
60	1				5					10					15	
	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
				20					25					30		
	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
			35					40					45			
65	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Gln	Leu	Cys	Thr	Val	Leu

	50		55		60	
	Ala Arg Ser Phe Ala Asp Ile Gly Asp Ile Val Arg Gly Lys Asp Leu					
	65		70		75	80
5	Tyr Leu Gly Tyr Asp Asn Lys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa					
		85		90		95
	Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa					
		100		105		110
	Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa					
		115		120		125
10	Phe Phe Gln Leu Arg Glu Asp Trp Trp Thr Ser Asn Arg Glu Thr Val					
		130		135		140
	Trp Lys Ala Leu Ile Cys His Ala Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa					
		145		150		155
	Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa					
15		165		170		175
	Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa					
		180		185		190
	Arg Trp Phe Glu Glu Trp Ala Glu Asp Phe Cys Arg Lys Lys Lys Lys					
		195		200		205
20	Lys Leu Glu Asn Leu Gln Lys Gln Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa					
		210		215		220
	Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa					
		225		230		235
	Thr Asn Cys Ser Val Trp Cys Arg Met Tyr Glu Thr Trp Ile Asp Asn					
25		245		250		255
	Gln Lys Lys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa					
		260		265		270
	Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa					
		275		280		285
30	Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa					
		290		295		300
	Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa					
		305		310		315
	Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa					
35		325		330		335
	Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa					
		340		345		350
	Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Cys					
40		355		360		

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 411 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

	Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
	1 5 10 15
60	Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
	20 25 30
	Ala Cys Ala Pro Tyr Arg Arg Leu His Val Cys Asp Gln Asn Leu Xaa
	35 40 45
	Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
	50 55 60
65	Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa

	65				70				75				80
	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Gln	Ile	Cys Thr
					85				90				95
5	Met	Leu	Ala	Arg	Ser	Phe	Ala	Asp	Ile	Gly	Asp	Il	Val Arg Gly Arg
				100					105				110
	Asp	Leu	Tyr	Leu	Gly	Asn	Pro	Gln	Glu	Xaa	Xaa	Xaa	Xaa Xaa Xaa Xaa
			115					120					125
	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa Xaa Xaa Xaa
		130					135					140	
10	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Asn	Asp	Pro	Glu	Phe	Phe	Lys Leu Arg
	145					150				155			160
	Glu	Asp	Trp	Trp	Thr	Ala	Asn	Arg	Glu	Thr	Val	Trp	Lys Ala Ile Thr
				165						170			175
15	Cys	Asn	Ala	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Cys	Xaa Xaa Xaa
				180					185				190
	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa Xaa Xaa
		195					200					205	
	Xaa	Xaa	Xaa	Xaa	Val	Pro	Gln	Tyr	Leu	Arg	Trp	Phe	Glu Glu Trp Ala
		210					215					220	
20	Glu	Asp	Phe	Cys	Arg	Lys	Lys	Asn	Lys	Lys	Ile	Lys	Asp Val Lys Arg
	225					230					235		240
	Asn	Cys	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Cys Xaa Xaa
				245					250				255
25	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa Xaa Xaa
			260						265				270
	Xaa	Xaa	Xaa	Xaa	Xaa	Cys	Ile	Ser	Cys	Leu	Tyr	Ala	Cys Asn Pro Tyr
			275					280					285
	Val	Asp	Trp	Ile	Asn	Asn	Gln	Lys	Glu	Xaa	Xaa	Xaa	Xaa Xaa Xaa
		290					295					300	
30	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa Xaa Xaa
	305					310					315		320
	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa Xaa Xaa
				325					330				335
35	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa Xaa Xaa
			340						345				350
	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa Xaa Cys Xaa
			355						360			365	
	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa Xaa Xaa
		370					375					380	
40	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa Xaa Xaa
	385					390					395		400
	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Cys	Xaa	Xaa	Cys		
				405					410				

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 411 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

60	Cys	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
	1				5				10				15		
	Xaa	Xaa	Cys	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
				20				25				30			
65	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa

		35				40			45							
	Xaa	Xaa	Val	Phe	Leu	Pro	Pro	Arg	Arg	Glu	His	Met	Cys	Thr	Ser	Asn
		50					55					60				
5	Leu	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
	65					70					75					80
	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
					85					90					95	
	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
				100					105					110		
10	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Ala	Met	Cys	Arg	Ala	Val	Arg	Tyr
			115				120					125				
	Ser	Phe	Ala	Asp	Leu	Gly	Asp	Ile	Ile	Arg	Gly	Arg	Asp	Met	Trp	Asp
	130						135					140				
15	Glu	Asp	Lys	Ser	Ser	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
	145					150					155					160
	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
					165					170					175	
	Xaa	Xaa	Xaa	Xaa	Xaa	Lys	Lys	Pro	Ala	Tyr	Lys	Lys	Leu	Arg	Ala	Asp
				180					185					190		
20	Trp	Trp	Glu	Ala	Asn	Arg	His	Gln	Val	Trp	Arg	Ala	Met	Lys	Cys	Ala
			195					200					205			
	Thr	Xaa	Xaa	Xaa	Xaa	Cys	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Ile	Pro
	210						215					220				
25	Gln	Arg	Leu	Arg	Trp	Met	Thr	Glu	Trp	Ala	Glu	Trp	Tyr	Cys	Lys	Ala
	225					230					235					240
	Gln	Ser	Gln	Glu	Tyr	Asp	Lys	Leu	Lys	Lys	Ile	Cys	Xaa	Xaa	Xaa	Xaa
					245					250						255
	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Cys	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Gly
				260					265					270		
30	Lys	Cys	Lys	Ala	Ala	Cys	Asp	Lys	Tyr	Lys	Glu	Glu	Ile	Glu	Lys	Trp
			275				280						285			
	Asn	Glu	Gln	Trp	Arg	Lys	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
	290						295					300				
35	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
	305					310					315					320
	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
					325					330					335	
	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
				340					345					350		
40	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Cys
			355				360					365				
	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Cys	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
	370					375					380					
45	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
	385				390					395						400
	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Cys	Xaa	Xaa	Cys						
				405					410							

(2) INFORMATION FOR SEQ ID NO:33:

50

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 311 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

55

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

60

(v) FRAGMENT TYPE: internal

(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

65

Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa

-84-

	1			5				10				15		
	Xaa	Xaa	Xaa	Xaa	Xaa	Ala	Cys	Met	Pro	Pro	Arg	Arg	Gln	Lys L u
				20				25					30	
5	Cys	Leu	Tyr	Ile	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
			35				40					45		
	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
			50				55				60			
	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
	65					70					75			80
10	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Gln	Phe	Leu	Arg	Ser	Met
				85					90				95	
	Tyr	Thr	Phe	Gly	Asp	Tyr	Arg	Asp	Ile	Cys	Leu	Asn	Thr	Asp
			100					105				110		
15	Lys	Lys	Gln	Asn	Asp	Val	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
			115					120				125		
	Xaa	Xaa	Xaa	Xaa	Xaa	Ser	Lys	Ser	Pro	Ser	Gly	Leu	Ser	Arg
			130				135				140			
	Trp	Trp	Lys	Thr	Asn	Gly	Pro	Glu	Ile	Trp	Lys	Gly	Met	Leu
	145					150					155			
20	Leu	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
				165							170			175
	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
			180					185				190		
25	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Lys	Pro	Gln	Phe	Leu	Arg	Trp	Met
			195				200					205		
	Trp	Gly	Glu	Glu	Phe	Cys	Ala	Glu	Arg	Gln	Lys	Lys	Glu	Asn
		210				215					220			
	Lys	Asp	Ala	Cys	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Cys	Xaa	Xaa
		225				230				235				240
30	Lys	His	Arg	Cys	Asn	Gln	Ala	Cys	Arg	Ala	Tyr	Gln	Glu	Tyr
				245					250					255
	Asn	Lys	Lys	Lys	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
			260					265				270		
35	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa
			275				280					285		
	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Xaa	Cys
		290				295				300				
	Xaa	Xaa	Xaa	Xaa	Cys	Xaa	Cys							
40		305				310								

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 7 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTISENSE: NO

(v) FRAGMENT TYPE: N-terminal

(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

Pro Arg Arg Gln Xaa Leu Cys
 1 5

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 20 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

CCRAGRAGRC AARAAYTATG

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

CCSMGSMGSC AGCAGYTSTG

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE: N-terminal
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

Phe Ala Asp Xaa Xaa Asp Ile
1 5

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

TTTGCWGATW WWSGWGATAT

20

(2) INFORMATION FOR SEQ ID NO:39:

- 5 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- 10 (ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
15 (vi) ORIGINAL SOURCE:
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

TTCGCSGATW WCSGSGACAT

20

(2) INFORMATION FOR SEQ ID NO:40:

- 20 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
25 (B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- 30 (ii) MOLECULE TYPE: peptide
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE: N-terminal
(vi) ORIGINAL SOURCE:
- 35 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

Pro Gln Phe Xaa Arg Trp
1 5

40 (2) INFORMATION FOR SEQ ID NO:41:

- (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
45 (B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
50 (iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

55

CCAWCKKARR AATTGWGG

18

(2) INFORMATION FOR SEQ ID NO:42:

- 60 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 18 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
65 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

CCASCCKGWAG AWCTGSGG

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE: N-terminal
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

Glu Trp Gly Xaa Xaa Xaa Cys
1 5

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

CAAWAWTCWT CWCCCCATTC

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA
(iii) HYPOTHETICAL: NO
(iv) ANTISENSE: NO
(v) FRAGMENT TYPE:
(vi) ORIGINAL SOURCE:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

CAGWASTCST CSCCCCACTC

WE CLAIM:

1. A composition comprising a nucleotide sequence of the *DBL* gene family, wherein said nucleotide sequence is selected from the group consisting of the *var-1*, *var-2*, *var-3* and *var-7* genes.

2. The composition of Claim 1, wherein the nucleotide sequence of the *var-1*, *var-2*, *var-3* or *var-7* gene encodes a cysteine-rich domain homologous to a cysteine-rich domain of a Duffy Antigen Binding Protein (DABP) derived from *Plasmodium vivax* and a Sialic Acid Binding Protein (SABP) derived from *Plasmodium falciparum*.

3. The composition of Claim 1, wherein the nucleotide sequence of the *var-1*, *var-2*, *var-3* or *var-7* gene encodes a cysteine-rich interdomain region between a first domain and a second domain.

4. The composition of Claim 1, wherein the nucleotide sequence is derived from a coding region of SEQ ID NO:13 or SEQ ID NO:15.

5. A composition comprising a polypeptide encoded by a nucleotide sequence of the *DBL* gene family, wherein said polypeptide is encoded by a *var-1*, *var-2*, *var-3* or *var-7* gene.

6. The composition of claim 5, wherein the polypeptide comprises a sequence of amino acid residues homologous to cysteine-rich domains of a Duffy Antigen Binding Protein (DABP) derived from *Plasmodium vivax* and a Sialic Acid Binding Protein (SABP) derived from *Plasmodium falciparum*.

7. The composition of claim 5, wherein the polypeptide comprises a sequence of about 300 to 400 amino acid residues occurring in the cysteine-rich interdomain region between a first domain and a second domain of a polypeptide encoded by the *var-1*, *var-2*, *var-3* or *var-7* gene.

8. The composition of claim 5, wherein the polypeptide comprises a sequence of amino acid residues of SEQ ID NO:14 or SEQ ID NO:16.

9. The composition of claim 5, wherein the polypeptide comprises a sequence of about 50 to about 325 amino acid residues of SEQ ID NO:14 or SEQ ID NO:16.

10. The composition of claim 5, wherein the polypeptide comprises a sequence of about 75 to about 300 amino acid residues of SEQ ID NO:14 or SEQ ID NO:16.

11. The composition of claim 5, wherein the polypeptide comprises a sequence of about 100 to about 250 amino acid residues of SEQ ID NO:14 or SEQ ID NO:16.

12. The composition of claim 5, further comprising a pharmaceutically acceptable carrier and an isolated Duffy Antigen Binding Protein (DABP) binding domain polypeptide, a Sialic Acid Binding Protein (SABP) binding domain polypeptide, or a combination thereof, in an amount sufficient to induce a protective immune response to *Plasmodium* merozoites in a mammal.

13. The composition of any of the preceding claims for use in inducing a protective immune response to *Plasmodium* merozoites in a mammal.

14. Use of the composition of any one of claims 1-12 in the preparation of a medicament for inducing a protective immune response to *Plasmodium* merozoites in a mammal.

15. A method of inducing a protective immune response to *Plasmodium* merozoites in a mammal, comprising administering to a mammal an immunologically effective amount of a pharmaceutical composition

comprising a pharmaceutically acceptable carrier and an isolated cysteine-rich polypeptide encoded by a *var* gene selected from the group of genes consisting of *var-1*, *var-2*, *var-3* and *var-7* genes.

16. The method of claim 15, further comprising administering to said mammal an immunologically effective amount of a Duffy Antigen Binding Protein (DABP) binding domain polypeptide, a Sialic Acid Binding Protein (SABP) binding domain polypeptide, or a combination thereof.
- 5

1/5

Family 1	DABP	C-X12-C-X5--VCIPDRRYQLCMKEL-X47-DFCKDIRWSLGFDDIIMGTMEGIGYSK-X11-
	SABP F1	C-X10-C-X9--VCIPDRRIQLCTIVNL-X36-KFCNDLKNSELDYGHLAGNDMDFGYST-X17-
	SABP F2	C-X13-C-X10-VCVPPRRQELCLGNI-X36-EVCKIINKTEADIRDIIGGTDYWNDSLNR-X15-
	EBL-e1	C-X12-C-X11-VCVPPRRQQLCLGYI-X36-KICNAILGSYADIGDIVRGLDVWRDINTN-X17-
Family 2	EBL-e2	-----ACAPYRRLHLCYDNL-X43-QLCTVLARSEADIGDIVRGKDLYLGYDNK-X37-
	Proj3 F1	C-X15-C-X15-ACAPYRRLHVCDQNL-X45-QICTMLARSEADIGDIVRGDLYLGNPQE-X30-
	Pr j3 F2	C-X17-C-X31-VFLPPRRHEMCTSNL-X55-AMCRVRYSEADLGDIIIRGRDMWDEDKSS-X32-
	Proj3 F3	C-X10-C-X10-ACMPRRRQKLCLYYI-X52-QFLRSMMYTEGDYRDICLNTDISKKQNDV-X15-
	E31a	C-X10-C-X11-ACIPRRRQKLCLHYL-X51-DFKRQMFYTEADYRDICLGTDISSKKDTS-X15-
Family 1	DABP	TDEKAQRRKQHNBSKAQIHTAMYSV-X11-C-X8--ePQIYRWIRENGRDYVSELPTEVQKLKEKC-X11--C-X1--
	SABP F1	SEHKIKNFRKEHNEPREKLHEMLSEH-X6--C-X6--eLQITQIHEHGEELLERNDRSKLPKSKC-X8--C-X0--
	SABP F2	NKKNDKLFREDHKKVKKDVNVISWVF-X5--C-X7--IPQFRHSENGDDYCDKTKMIETLKVEC-X4--C-X1--
	EBL-e1	KKQNDNERNKWEKQNLHSSMVKHI-X5--C-X8--IPQFLRHLKEWGEFCEEMGTEVKQLEKIC-X4--C-X1--
Family 2	EBL-e2	KGDFQFLREDHHTSNRETVMKALICHA-X11-C-X23-VPQYLRFEEWAEDFCRKKKKKLENLQKQC-X6--C-X15-
	Proj3 F1	NDPEFFKLREDHHTANRETVMKAITCNA-X9--C-X23-VPQYLRFEEWAEDFCRKKKKKIDVKRNC-X12--C-X22-
	Proj3 F2	KKPAYKKLRADHHEANRHQVHRAMKCAT-X4--C-X8--IPQRLRWMTWEAEWYCKAQSQEYDKLKKIC-X11--C-X6--
	Proj3 F3	SKSPSGLSRQEHKTKNGPBIHKGMLCAL-X37-----KPOFLRMIENGEEECABRQKKEI IKDAC-X8--C-X3--
	E31a	KISNSIRYRKSHMETNGPVIHEGMLCAL-X42-----RPOFLRHLTEGENEKECKEYKVLAKC-X11--C-X3--
Family 1	DABP	VPQCQACKSXDQ
	SABP F1	WITRKN-X56-----CX--C
	SABP F2	WIRSKP-X41-C-X7-----CX--C
	EBL-e1	WISKKK-X36-C-X20-----CXX-C
		WIKERN-X38-C-X19-----CXX-C
Family 2	EBL-e2	CTNCSVWCMRYET
	Pr j3 F1	WIDNKK-X68-C-X30-----CXX-C
	Pr j3 F2	WINNOKE-X69-C-X40-----CXX-C
	Proj3 F3	CGKCKAACDKYKEBIEKNEQWRK-X73-C-X6-C-X30-CXX-C
	E31a	YVENKKK-X43-C-X4-----CX--C
		WIGIWD-X42-C-X8-----CXXC

FIG. 1

2/5

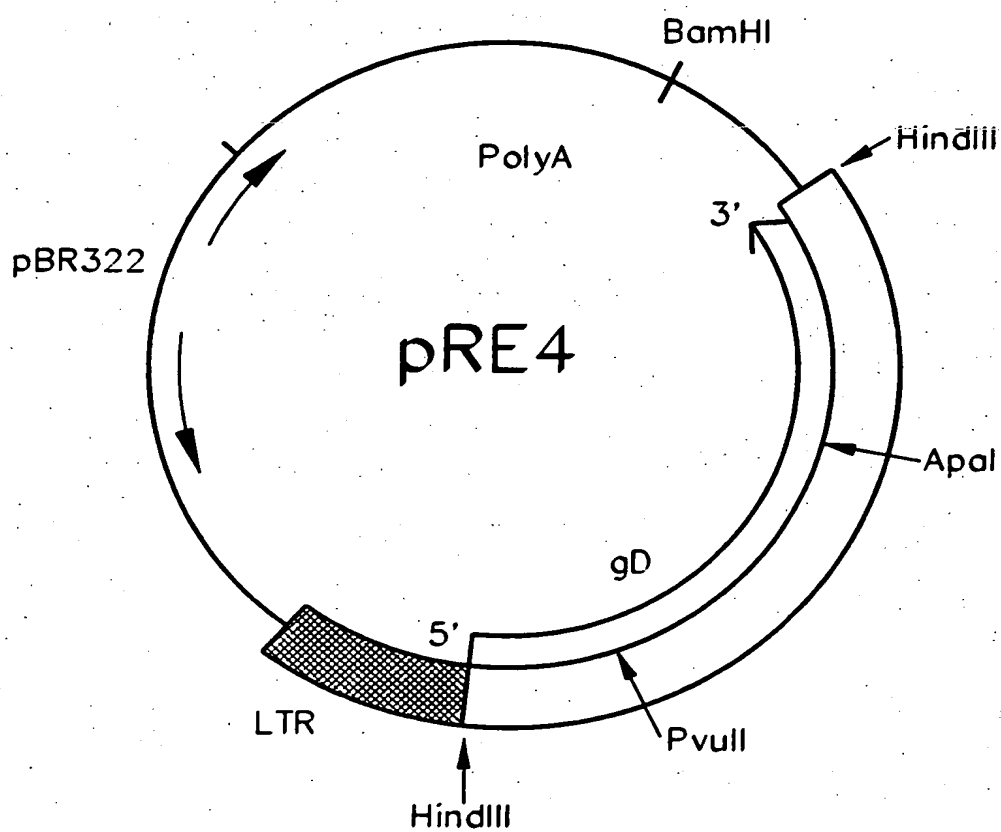


FIG. 2

3/5

FIG. 3

Consensus amino acid sequences and the synthetic oligonucleotide primers designed from them.

UNIEBP5 and 5A: P R R Q K/E L C

UNIEBP5, for A+T biased codon usage:
CC(A/G)-AG(G/A)-AG(G/A)-CAA-(G/A)AA-(C/T)TA-TG

UNIEBP5A, for G+C biased codon usage:
CC(C/G)-(C/A)G(C/G)-(C/A)G(C/G)-CAG-CAG-(C/T)T(C/G)-TG

UNIEBP5 B and C: F A D I/Y G/R D I

UNIEBP5B, for A+T biased codon usage:
TTT-GC(A/T)-GAT-(A/T)(A/T)(A/T)-(G/C)G(A/T)-GAT-AT

UNIEBP5C, for G+C biased codon usage:
TTC-GC(G/C)-GAT-(A/T)(A/T)C-(G/C)G(G/C)-GAC-AT

UNIEBP3 and 3A: P Q F L/F R W

UNIEBP3, for A+T biased codon usage:
CCA-(A/T)C(T/G)-(T/G)A(A/G)-(A/G)AA-TTG-(A/T)GG

UNIEBP3A, for G+C biased codon usage:
CCA-(C/G)C(G/T)-G(A/T)A-GA(A/T)-CTG-(C/G)GG

UNIEBP3 B and C: E W G D/E D/E Y/F C

UNIEBP3B, for A+T biased codon usage:
CA-A(A/T)A-(A/T)TC-(A/T)TC-(A/T)CC-CCA-TTC

UNIEBP3C, for G+C biased codon usage:
CA-G(A/T)A-(G/C)TC-(G/C)TC-(G/C)CC-CCA-CTC G+C Biased

4/5

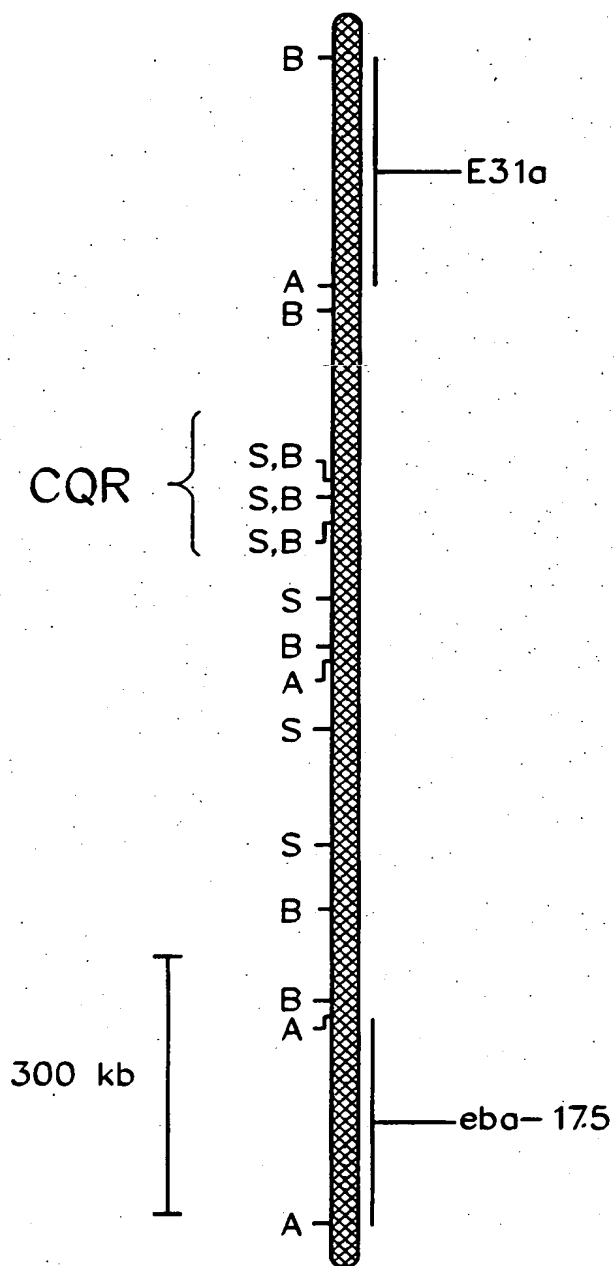


FIG. 4

SUBSTITUTE SHEET (RULE 26)

5/5

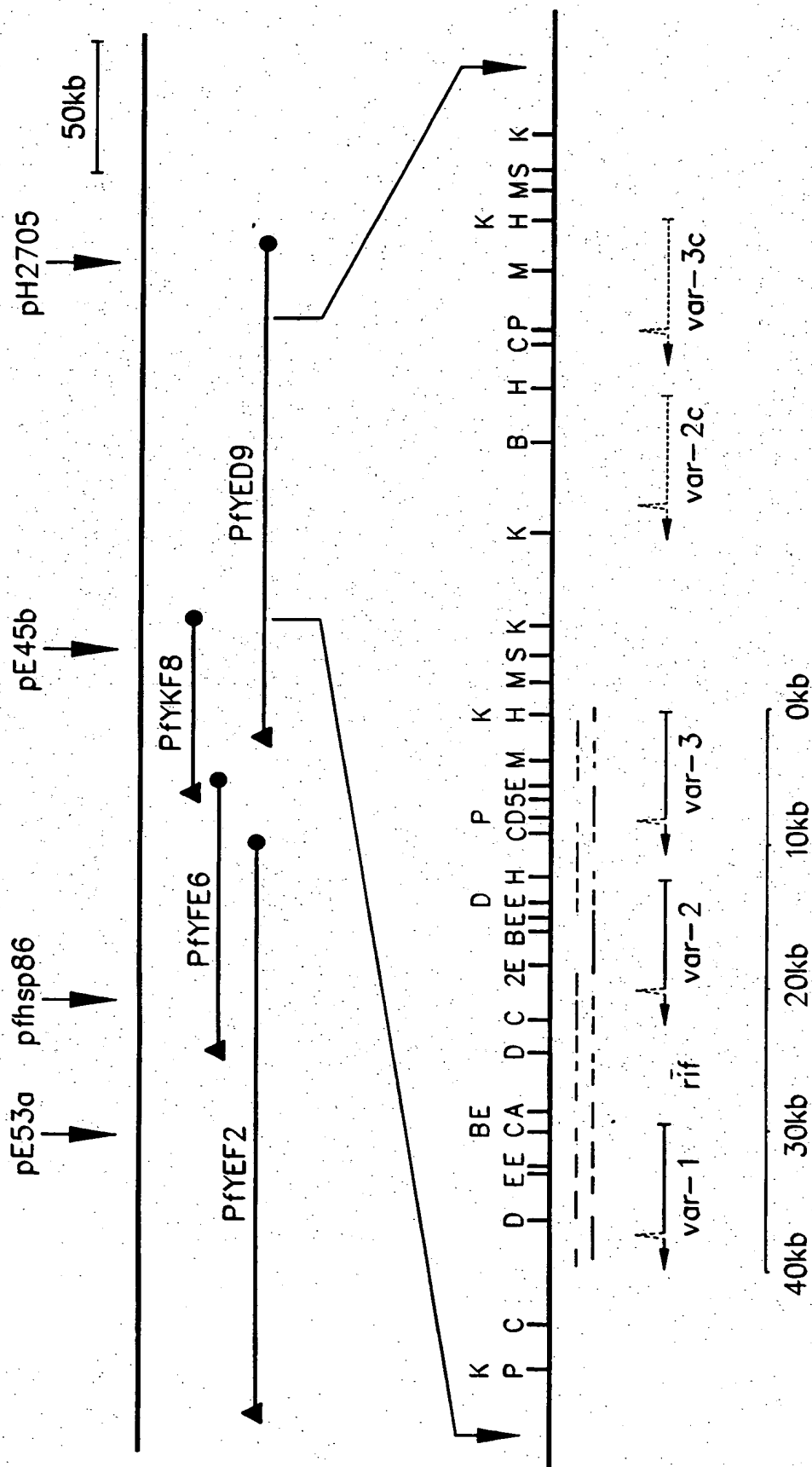


FIG. 5



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification⁶ : C07K 14/445, C12N 15/30, A61K 39/015	A3	(11) International Publication Number: WO 96/40766 (43) International Publication Date: 19 December 1996 (19.12.96)
(21) International Application Number: PCT/US96/09508 (22) International Filing Date: 7 June 1996 (07.06.96) (30) Priority Data: 08/487,826 7 June 1995 (07.06.95) US (71) Applicant: THE GOVERNMENT OF THE UNITED STATES OF AMERICA, represented by THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES [US/US]; Office of Technology Transfer, National Institutes of Health, Suite 325, 6011 Executive Boulevard, Rockville, MD 20852-3804 (US). (72) Inventors: SIM, Kim, Lee; 308 Argosy Drive, Gaithersburg, MD 20878 (US). CHITNIS, Chetan; 3217 Wisconsin Avenue, No. 2B, Washington, DC 20016 (US). MILLER, Louis, H.; 5450 Whitley Park Terrace, No. 609, Bethesda, MD 20814 (US). PETERSON, David, S.; 315 Edmonston Drive, Rockville, MD 20851 (US). SU, Xin-Zhuan; Apartment 1122, 1001 Rockville Pike, Rockville, MD 20852 (US). WELLEMS, Thomas, E.; 1715 Wilmart Street, Rockville, MD 20852 (US).		(74) Agent: ALTMAN, Daniel, E.; Knobbe, Martens, Olson and Bear, 16th floor, 620 Newport Center Drive, Newport Beach, CA 92660 (US). (81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 6 February 1997 (06.02.97)
(54) Title: BINDING DOMAINS FROM PLASMODIUM VIVAX AND PLASMODIUM FALCIPARUM ERYTHROCYTE BINDING PROTEINS (57) Abstract <p>The present invention provides isolated polypeptides useful in the treatment and prevention of malaria caused by <i>Plasmodium falciparum</i> or <i>P. vivax</i>. In particular, the polypeptides are derived from the binding domains of the proteins in the DBL family as well as the sialic acid binding protein (SABP) on <i>P. falciparum</i> merozoites. The polypeptides may also be derived from the Duffy antigen binding protein (DABP) on <i>P. vivax</i> merozoites.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

INTERNATIONAL SEARCH REPORT

Inter. Application No

PCT/US 96/09508

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K14/445 C12N15/30 A61K39/015

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,95 07353 (THE GOVERNMENT OF THE UNITED STATES OF AMERICA) 16 March 1995 see the whole document ---	1-16
A	SCIENCE, vol. 264, 1994, pages 1941-1944, XP002021139 K. SIM ET AL.: "Receptor and ligand domains for invasion of erythrocytes by Plasmodium falciparum" ---	
A	J. EXP. MED., vol. 180, 1994, pages 497-506, XP000615205 C. CHITNIS ET AL.: "Identification of the erythrocyte-binding domains of Plasmodium vivax and Plasmodium knowlesi proteins involved in erythrocyte invasion" --- -/--	



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

13 December 1996

Date of mailing of the international search report

07. 01. 97

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+ 31-70) 340-3016

Authorized officer

Skelly, J

INTERNATIONAL SEARCH REPORT

onal Application No
PCT/US 96/09508

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	<p>CELL, vol. 82, 1995, pages 89-100, XP002021140 X. SU ET AL.: "The large diverse gene family var encodes proteins involved in cytoadherence and antigenic variation of Plasmodium falciparum-infected erythrocytes" see the whole document ---</p>	1-16
T	<p>CELL, vol. 82, 1995, pages 1-4, XP002021141 P. BORST ET AL.: "Antigenic variation in malaria" -----</p>	

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 96/09508

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Please see Further Information sheet enclosed.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 96/ 09508

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

Remark : Although claims 15 and 16 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

information on patent family members

PC T/US 96/09508

**Patent document
cited in search report**

WO-A-9507353

Publication
date

16-03-95

Patent family member(s)

AU-A-	7872194
EP-A-	0719333

Publication date

27-03-95
03-07-96

THIS PAGE BLANK (USPTO)